

**MOBILE HEALTH (mHEALTH) ASSESSMENT OF ILLICIT DRUG USE
AMONG COMMUNITY DWELLING DRUG USERS IN
BALTIMORE, MD**

By
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Abstract

Background: Substance abuse is a chronic disease often characterized by multiple attempts at abstinence, frequent relapse and is associated with a range of morbidities and mortality. This dissertation utilizes a mobile health (mHealth) data collection method known as Ecological Momentary Assessment (EMA) to capture the dynamic process that drug use represents. The goals of this dissertation were to examine the accuracy of real-time mHealth methods in assessing drug use, examine individual drug using patterns to identify those at risk for poor engagement in care and to examine the real-time environments of drug using and craving.

Methods: Exposure Assessment in Current Time (EXACT) study participants were recruited from the AIDS Linked to the IntraVenous Experience (ALIVE) study, an on-going, community-recruited, observational cohort of persons with a history of injecting drugs in Baltimore, MD. The EXACT study included four successive trials, planned to follow 30 participants each for 30 days and was conducted from November 2008 through May 2013. Participants were asked to self-initiate a survey and self-report through a hand-held device each time they either craved (but refrained from using) or used heroin or cocaine (or both) in any manner (smoked, snorted or injected). At the end of each week, sweat patch samples (*PharmCheck*®) were collected for measurement of illicit substances and participants answered an audio-computer assisted self -interview (ACASI)

questionnaire concerning activities, behaviors and drug using events during the prior week.

Results: 109 EXACT participants were a median of 48.5 years old, 90% African American, 52% male and 59% HIV-infected. EMA methods demonstrated moderate percent agreement of reported drug use when compared to ACASI methods but less agreement when compared to sweat patch methods. Real-time collection of drug use identified three distinct classes of drug users. The most risky class included individuals engaging consistently in high-intensity drug using behavior, which was associated with poor engagement in care. Lastly, drug-related activities provided the strongest cues for real-time drug use, while craving was associated with being in more structured environments.

Conclusion: Interactive mHealth methods are capable of assessing and describing the drug-using environment and can provide the framework for developing context-sensitive interventions (ecological momentary interventions) that can be tailored to prevent relapse and support cessation of illicit drug use.

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Completing a PhD far exceeds the written words on the pages of the dissertation.

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Chapter 1:

Introduction and Review of Literature

Background

Substance abuse is a chronic disease often characterized by multiple attempts at abstinence with frequent relapse. Individuals with substance abuse problems tend to have a range of vulnerabilities that place them at increased risk for relapse as well as becoming HIV infected and failing to achieve the desired treatment outcome of viral suppression [1, 2]. People who inject drugs (PWID) are often poorly engaged in care due to multiple factors impeding their success [2], including continual risky drug using practices, HIV infection, hepatitis C infection, homelessness, depression, violence, poverty, incarceration, and poor treatment outcomes [1, 3, 4]. Yet, studies have found that among PWID capable of sustaining high levels of adherence can demonstrate positive HIV treatment outcomes [5].

Identifying factors associated with drug use and relapse as well as understanding the pathways leading to drug use requires accurate exposure ascertainment methods. Self-reports of drug use are subject to socially desirable reporting. Despite substantial research, identification of the proximate predictors of relapse to illicit drug use, non-adherence to HIV medications, or to disengagement with primary care among drug users remains elusive. Understanding the dynamics of drug use (individual and situational) will aide in answering questions including: why are some active drug users able to maintain cessation and do well on HIV

treatment while others have difficulty with drug relapse, ART non-adherence and virologic failure.

Clinic-based, individualized support delivered by case managers or patient navigators has been shown to improve engagement in HIV care for many patients including PWID, but few settings have resources to offer such intensive treatment to all who need it [6]. Ecological momentary assessment (EMA) methods collect participant-level data in real time and facilitate responsive communication between providers and patients. EMA is a mobile health (mHealth) method that employs mobile devices (e.g., smartphones or other hand-held devices) to improve health outcomes, healthcare services and public health research. mHealth methods, such as Short Message Service (SMS) text messages have proven effective at increasing attendance at clinic appointments and improved adherence through antiretroviral (ART) dose reminder messages [7-12].

Newer technologies are able to collect patient-level data in real time and facilitate responsive communication between clinic and patient. This dissertation utilizes data collected using ecological momentary assessments among a sample of drug users from the Exposure Assessment in Current Time (EXACT) study to examine the accuracy of real-time mHealth methods in assessing drug use, to identify individual drug using patterns to identify those at risk for poor engagement in treatment and care and to examine the real-time correlates of drug use and craving.

Injection Drug use in the United States

It has been estimated that approximately 16 million (range 11-21 million) individuals aged 15-64 years inject drugs worldwide [13]. In 2012, approximately 7 million Americans aged 12 or older used cocaine or heroin in the past month and approximately 2 million Americans injected these drugs [14]. Needle sharing among persons who inject drugs (PWID) is a leading risk factor for the acquisition of HIV, hepatitis B and C as well as endocarditis and sepsis [15, 16]. Age-adjusted mortality rates among PWID are estimated at 14 times that of non-injection drug users, with deaths attributed to drug overdose, suicide, and AIDS-related illness [17]. Homelessness, depression, violence, poverty, and incarceration are all associated with drug use, which often results in a loss of productivity, troubled families and unsafe communities [3, 18, 19].

Injection Drug Use in Baltimore, MD

Baltimore City has one of the highest rates of PWID per capita in the United States [20]. It is estimated that 1 in 8 adults in Baltimore are heroin dependent and the city is ranked first in the nation for heroin and crack-related emergency room (ER) visits [21]. Surveillance data from 2012 reported 54% of prevalent HIV diagnoses were among injection drug users, making injection drug use the most common risk group for new diagnoses in Baltimore [22]. Currently, it is estimated

that 1 in 10 African American males age 50-59 in Baltimore is living with HIV [22, 23].

Disorder, Chaos and Injection Drug Use.

Illicit drug use represents a dynamic process resulting from a complex interplay of factors occurring at multiple levels. Persons affected by substance abuse often suffer from maladaptive, drug-seeking behaviors and material deprivation that put them at risk for acquiring several diseases, including HIV, hepatitis C (HCV) [24-27] and tuberculosis [28, 29]. In addition to risky drug using behaviors, people who inject drugs are known to also engage in risky sexual behaviors, and suffer from high rates of depression [30-32] and alcohol dependence [32, 33]. These individual characteristics may be responsible for risk taking behaviors, however they do not explain all the inter-personal variability in risk behavior [34]. Aside from behavioral characteristics of drug users, substance abuse is also commonly associated with features of a chaotic or disordered life. This includes financial and legal difficulties as well as inadequate housing or transportation [35-37]. For example, a recent study demonstrated the relationship between levels of income inequality and the likelihood of fatal drug overdose [38].

Additional contextual factors associated with a disordered life and HIV risk behavior include situational factors (e.g., availability of services or employment

and current emotional state), social norms and attitudes, and features of the physical environment (e.g. housing quality) [34]. Characteristics of neighborhoods have been shown to be important determinants of the health of drug users. Recent research in Baltimore, MD examined the association between both neighborhood deprivation [39] and residential rehabilitation (defined as the percentage of residential properties where investment in interior or exterior maintenance exceeded \$5000 USD for a given year)[40] on injection cessation. Continuous residence within neighborhoods with moderate/high rehabilitation and relocating to neighborhoods with moderate/high rehabilitation, were associated with a lower likelihood of injection drug use, while individuals who relocated from highly deprived to less deprived neighborhoods experienced a strong positive impact on long-term injection cessation.

However, a primary challenge faced by neighborhood research is answering not just *whether*, but also *how*, the neighborhood influences drug use [41]. Few studies have assessed specific pathways from neighborhood environment to drug-related outcomes [42]. It has been suggested that macro-level neighborhood exposures, such as area-level deprivation, may be linked to drug-related outcomes through psychological and physiological stress [43, 44]. As a result, drugs are often used to relieve stress [42]. Previous research has shown that the level of psychological distress among residents partially mediated the observed relation between neighborhood deprivation and drug use in a sample of adults from Detroit [45].

Similarly, in Baltimore, injection drug users in more disordered neighborhoods have been shown to have higher levels of depression, and that this depression was associated with greater injection frequency [46].

It has been postulated that intra-urban differences in the availability of illicit substances may be one of the key determinants linking neighborhood-level characteristics to individual drug-related outcomes. There are likely multiple pathways through which neighborhood-level factors influence drug use; the psychosocial environment and the local drug environment are both necessary to understand in order to know how neighborhood context influences drug-related outcomes.

Drug craving has also been theorized to have a critical role in drug dependence and relapse, although there have been substantial inconsistencies in data supporting this view [47, 48]. There is clear recognition of the need for more detailed and novel methods for measuring craving (e.g., a virtual reality approach has been used to examine cue-elicited tobacco cravings [49]).

Despite much research concerning illicit drug use and its associated behaviors, novel strategies are needed to better understand the drug-using environment and to identify the proximate determinants of drug use of marginalized populations.

Injection drug use, HIV and engagement in care

The Health Resources and Services Administration (HRSA) propose a continuum of engagement in HIV care. According to HRSA, optimal HIV care includes early diagnosis of infection, prompt linkage to a regular source of care, appropriate initiation of antiretroviral therapy (ART), high levels of medication adherence and retention in care over the life course [50]. Adherence is defined as the percentage of prescribed pills taken by the patient, yet pill taking is only one of several behavioral factors of medication adherence. Active abuse of crack/cocaine has been associated with poor engagement in care and is commonly associated with features of a disordered life. Regardless of HIV status, engagement in health care entails specific actions that individuals must take to achieve the best outcomes from available health care services [51]; for example, having a primary care physician and regularly attending outpatient appointments rather than utilizing the emergency department for primary care needs (which is exceedingly expensive) .

Previous clinic-based and community cohort studies of injection drug users showed the greatest risk factors for failure to suppress HIV RNA to be low social support [52] and missed clinic appointments [53], while ART use was independently associated with increases in patient-provider engagement, stable housing and a positive attitude about ART benefits, even if using illicit drugs [54]. Out-of-care people living with HIV/AIDS (PLWHA), particularly those who inject drugs, face several barriers that keep them from taking their medication regularly

such as continued drug use, a lack of access to outpatient care and physician concern of ART resistance due to non adherence and incarceration [52, 55-57]. New strategies to better understand drug use and barriers to care are necessary for PWIDs to not only remain adherent to their ART regimens, but engaged in care overall.

Assessment of illicit drug use

Reliance on self-reported behaviors by drug users is common in epidemiologic studies. In the field, self-reports are often the only feasible method for capturing drug use and its related behaviors. In cohort studies, illicit drug use is often self-reported over extended periods of recall (e.g., 6 to 12 months) [4, 54, 58]. There are several methods for self-reporting drug use including face-to-face interviews as well as audio-computer assisted self-interviews (ACASI) [59, 60].

Face-to-face interviews, although fairly cheap, do increase the likelihood of social desirability bias and individuals tend to underestimate drug use. Social desirability bias is a reporting bias that arises when individuals under report specific behaviors or actions because they believe they are sensitive and not socially acceptable [61]. ACASI methods were created to address this issue and decrease social desirability bias by allowing greater respondent privacy. When using ACASI, questions are administered audibly and in text on a computer screen in a private room without the direct participation of a study interviewer [62]. Historically, ACASI has

resulted in greater disclosure of sensitive information such as, illicit drug use, age of onset of injecting, injecting practices, rates of sharing syringes and risky sexual behaviors (e.g. condom usage and frequency of unprotected sex) [62-64].

Additionally, the use of ACASI methods tend to reduce the amount of missing data because it is thought that the simultaneous use of visual and verbal cues (computer screens and recorded speakers) encourages participants to pay greater attention to the questions [63].

ACASI-based methods do share the same limitations as face-to-face interviews. Despite the ability to capture information on sensitive information, recall bias remains a problem. Questions concerning duration, frequency and amount of drug use are difficult to remember when assessed every 6-months (the traditional study visit interval of epidemiologic studies). Additionally, both under and over reporting of drug use behaviors occurs because of long periods of time between study visits.

Biological samples of hair, urine, sweat or blood assess the biochemical markers of drug use, are considered more accurate than self-report and the recognized gold standard in estimating illicit drug use [65]. The utility of these methods lies in their ability to detect the length of time drugs have been in the body (depending on the biological specimen) and are widely used in drug testing and treatment settings.

Urine toxicology testing has been the most commonly practiced method of drug screening in the workplace, criminal justice system and drug treatment settings over the past two decades because of the wide array of drug types easily detected by urinalysis [66]. Urinalysis has good sensitivity and specificity for the detection of recent drug use (e.g., detection of opiate or cocaine use within the past 24-48 hours [67]). However, to determine an individual's use pattern, urine collection would be required every 2-3 days. Additional limitations of urinalysis include the difficulty of obtaining a spontaneous sample, the invasive nature of testing and the short detection window. This short detection window is problematic when there is less frequent contact with participants, as is often the case with epidemiologic studies and outpatient treatment settings [68].

Sweat patches are another method for detecting drugs in the body. They are a convenient, less invasive method with a longer window of detection for assessing drug use. Similar to urinalysis, drugs detected in sweat include the 'parent drugs' (the same chemical compound that was taken by the drug user) and drug metabolites (breakdown products of the parent drug) and are excreted by sweat glands. Unlike urinalysis, which reports drug use as positive or negative based on the presence of metabolites at a standard quantity cut off of 300 ng/ml, sweat patches are able to describe drug use by quantifying the amount of metabolites in the sweat over the duration of wear at 10 ng/ml [67]. The utility of the patch is that

it can be worn for up to 10 days and is able to capture any drug use that occurred during the period of wear as well as the 24 hours prior to patch application. However, sweat patches do not capture as many drug types as urinalysis. The patch is designed to be flexible, waterproof, and safe from environmental contaminants [69] but can be easily removed. In fact, once the patch comes off the skin, it cannot be put back on the skin and resume drug use capture. Despite being the gold standard for the assessment of drug use, biological samples remain difficult to collect in the field, can be cost prohibitive and require substantial participant engagement (e.g. weekly returns to treatment facility for urine test or patch removal).

Reliability and validity of self-reported and biological methods of drug use assessment

The reliability of a test refers to the extent that it has overall consistency. Parallel forms of reliability refer to whether different versions of an assessment tool produce similar results under consistent conditions (i.e., repeatability). For example, do self-reports of drug use match the reports of biologic sample or ACASI reports? The validity of a measurement tool describes the degree to which it is able to scientifically answer the question it is intended to answer (e.g., does urinalysis actually capture recent drug use?). Concurrent validity is a type of validity that is demonstrated when a test correlates well with a measure that has been previously validated. These measurement properties are independent of one

another; a measurement may be valid but not reliable or reliable but not valid.

With respect to assessing drug use, biologic samples (including sweat patch and urinalysis) and self-reports via face-face interview or ACASI have been previously described as valid and reliable measures [70, 71]; however, mixed results have been described when these methods are compared to one another and vary depending on the drug being investigated.

Studies examining the validity and reliability of sweat patch methods have examined the correlation between patch and urine results as well as a participant's self-reported frequency of use. Prior validation studies using sweat patches and known doses of cocaine and heroin describe the patch sensitivity and specificity for cocaine as 86% and 97% [72] and 87% and 93% for heroin [73]. A 10-week outpatient clinical trial in which participants wore sweat patches, provided urine samples and self-reports of cocaine use thrice weekly, demonstrated the concurrent validity of urine and sweat patches to be reasonable (correlation: 0.76, $p < 0.001$), but the correlation between self-report and the patches to be lower (correlation: 0.40, $p < 0.05$) [67]. In this study, the authors used urinalysis as the previously validated measure of assessing drug use. A separate outpatient study examining the utility of sweat testing for monitoring drug use found the level of agreement between positive sweat test results and positive urine results to be 33% for heroin and 92% for cocaine. When compared to self-reports, sweat patches were positive in 32% of cases reporting recent heroin use and 91% of cases

reporting recent cocaine use. Comparisons of urine toxicology screens and patient self-reports showed that self-reports matched urine results in 88% of cases of heroin use and 78% of cases of cocaine use [68]. The analysis clearly demonstrates that the parallel reliability of these methods is not only different depending on which methods are being tested but the reliability also differs according to the drug being tested.

The ability to accurately assess illicit drug use remains difficult in epidemiologic studies despite the many methods available. Yet, self-reported drug use remains the most widely employed method of assessing drug use. This is because studies continue to demonstrate drug users' ability to provide sufficient, reliable, and valid descriptions of their drug use and its context, whereas biological samples only assess biological markers of drug use itself [71].

Mobile Health (mHealth)

The use of mobile phones for communication and access to information via the Internet has become nearly ubiquitous in both low- and high-income countries. At the end of 2013, the number of active mobile phone subscriptions was estimated at 6.8 billion worldwide, or approximately 96 subscriptions for every 100 inhabitants of the world [74]. As of early 2014, cell phone ownership among adults in the United States exceeded 90% and 58% had a smart phone [75]. In the foreseeable future, the majority of the world's population will have access to the Internet via a

mobile device. With this expanded accessibility of increasingly powerful handheld devices has come recognition of potential applications for improving health and health care [76].

mHealth is defined by the Global mHealth Alliance as the practice of medicine and public health through the usage of mobile devices. Mobile devices include Portable Digital Assistants (PDAs), mobile phones or tablet computers for data collection, health services, and treatment support and information dissemination. The promise of mobile health technologies for strengthening health care delivery in resource-limited settings has been acknowledged by the United Nations Joint Programme on HIV/AIDS (UNAIDS) in development of its strategic plan [77]. mHealth is currently being used for health education and awareness, remote data collection and monitoring, communication and training for healthcare workers, disease and epidemic outbreak tracking and diagnostic and treatment support [78].

Use of mHealth in Research Settings

Researchers and patients have begun to use mHealth to explore the potential for mobile technologies to improve health outcomes and lower costs by increasing patient engagement, improving provider quality, and optimizing efficiency in health care [79]. The rise of mHealth research began with a focus on text messaging. Text messaging has been effectively utilized to provide decision support to frontline health workers, to remind patients of appointments, and

improve attendance at clinic appointments [80-83]. It has also been extensively used for the management of HIV treatment and care as well as for weight management, cognitive behavioral therapies, sexual health, and the control of diabetes [84-87].

Prior to text messaging, behavioral interventions to promote adherence to antiretroviral therapy among HIV infected individuals included the use of alarm devices or counseling sessions with the hopes of creating individualized interventions to increase adherence. One study, a four arm randomized clinical trial (RCT) in Kenya, examined the differences in counseling alone, a pocket electronic pill reminder, counseling plus the pill reminder or neither on time to virologic suppression and percent adherence to ART. Participants were followed for 18 months after ART initiation; those receiving counseling were less likely to have monthly adherence <80% and there was no impact of alarm use on poor adherence [88].

Text messaging has been used for ART dose reminder messages in several settings to improve adherence [9-11]. Two randomized controlled trials (RCTs) of mHealth in Sub-Saharan Africa have demonstrated benefit of weekly text messages for improving adherence [7, 8] and rates of viral suppression [8]. A meta-analysis of these RCT studies in Kenya demonstrated that any weekly text-

messaging (long or short) was associated with a lower risk of non-adherence at 48-52 weeks (RR 0.78, 95% CI 0.68-0.89) [12].

More recently, sophisticated mobile devices (e.g., accelerometers to measure physical activity and sensors to measure heart rate, blood pressure, or other biological processes) have arisen from the built-in computer chips and geographic sensing power of newer mobile technologies [79]. These systems have enabled health researchers to define profiles of behaviors and risk exposures with more granularity in real-time. These noninvasive devices and sensors allow physiology to be monitored continuously with little to no engagement by the individual. Combining these technologies with traditional text messaging that inquire about behaviors, mood or location offer new epidemiological methods for assessing daily behavioral cues and activities.

Despite the increasing availability and enthusiasm for mHealth tools, evidence-based research to understand substance-using populations remains limited. Early use of mHealth methods among substance using populations showed that in substance abuse treatment settings, active cocaine and heroin users can reliably report mood and drug use triggers using electronic handheld diaries [89, 90].

Ecological Momentary Assessment

Traditional data collection methods of cohort studies require participants to attend study sites every 6 months (although this time interval can vary) to answer questionnaires/surveys concerning events in those past 6 months. At best, data is obtained twice a year if a participant is retained in the study.

Ecological momentary assessment (EMA) methods utilize smart phones or hand held devices to collect data concerning study participants; these technologies may be the participant's personal phone or provided by the study. Typically in EMA studies, momentary assessments are ascertained when the provider or investigator sends electronic prompts to participants for immediate response randomly throughout the day (typically waking hours 7am-10pm, at which point the device can be charged and/or turned off for the day), known as the random-prompt responses. Additionally, participants are required to self-cue and self-report through the mobile device when an event occurs, known as event-contingent responses. The random prompts enable assessment of the base rates of exposure to possible relapse precipitants such as cues and stressors [91]. Data collected through random prompts also enables a truly prospective approach to the question of what events preceded a specific event episode. The event-driven data provide near real time self-report of such episodes.

The hand held-devices are sometimes also equipped with global positioning systems (GPS), which allow for continual data collection of the participants location at the time of the reported event. The two-way communication is how EMA allows for real-time data collection on any activity or mood. Utilizing EMA methods of real-time data collection, sociodemographic, behavioral and situational factors can be more precisely measured.

Ecological Momentary Assessment and substance abuse

EMA methods have been used in behavioral research concerning smoking cessation, weight loss and recently, cravings of heroin and cocaine [89, 92-94]. Epstein and Preston were some of the early adopters in using EMA methods to study drug-using populations in the U.S. An initial study utilizing EMA with Personal Digital Assistants (PDAs), examined how smoking was related to other drug use and craving during daily life. It was found that smoking frequency increased with increased reports of tobacco, cocaine and heroin cravings captured through the random-prompts, while smoking and tobacco cravings were reduced during periods of urine verified abstinence from cocaine [92].

In a separate study, data were collected among methadone-maintained outpatient participants during urine-verified periods of use and abstinence to further understand patterns of daily illicit drug use. Periods of cocaine use were associated with idle and solitary afternoons, and also associated with a greater likelihood of

early-morning or late-evening work. Additionally, several measures of negative mood increased during abstinence [89]. The aim of this study was to examine distinct patterns of mood and behavior to inform treatment interventions aimed at changing daily activities.

To examine stress's role on drug use, Preston et al. used EMA data collected from methadone-maintained cocaine and heroin users who provided ratings of stress which were compared to those of craving and mood in the hours prior to drug use. Stress was shown to have a significantly positive relationship with current cravings of cocaine and heroin and was greater in entries in which participants also reported past-hour exposure to negative-mood triggers of sadness and boredom [95].

These studies were novel as they used EMA to examine the “situatedness” of drug use, the context in which drug use occurred and how mood affected drug use. The real-time nature of data collection using EMA also provides for the examination of the main exposures that precede events of interest. Utilizing the same population of methadone-maintained cocaine and heroin outpatients, Epstein et al examined changes in reports of mood and exposure during the 5 hours preceding each self-reported episode of drug use or craving [90]. Cocaine use was statistically significantly associated with increases in participant reports of “seeing the drug”, being “tempted out of the blue” and “wanting to see what would happen if I used”,

whereas heroin craving was statistically significantly associated with increased reports of feeling sad or angry. Neither cocaine craving nor heroin use showed associations with the triggers assessed [90].

Each of these studies demonstrated the ability of polydrug using individuals' ability to provide behavioral data during their daily life, the feasibility of using hand-held devices as well as the ability to consistently respond to questions concerning their drug use. It is for these reasons that ecological momentary assessment is regarded as a more precise measure of experienced well-being [96].

Goals of the dissertation

Current methods for assessing drug use rely heavily on drug type and manner of use often over prolonged intervals of follow-up. These methods miss varying periods of intense or intermittent use and further fail to capture the proximate context of an individual's drug using experience. The goal of this dissertation was to examine the drug-using environment of chronic illicit drug users in their natural settings (rather than a clinical or drug treatment population) using an interactive mobile health method. Using ecological momentary assessment data, this dissertation aimed to assess the concordance of assessing drug use via EMA methods to biological and ACASI methods, describe drug-using patterns and their association with engagement in care and assess the situational and psychosocial triggers of drug use.

This dissertation examined the drug using and craving behaviors of participants from The Exposure Assessment in Current Time (EXACT) Study. EXACT participants were recruited from The AIDS linked to the Intravenous Experience (ALIVE), an on-going, community-recruited, observational cohort study of persons with a history of injecting drugs in Baltimore [97]. The ALIVE cohort is community- rather than clinic-based, thereby avoiding selection bias toward persons seeking or accessing care [97, 98]. Details of the EXACT study have been previously described [99], and included four successive trials conducted from November 2008 through May 2013. Each trial was planned to follow 30 participants each for 30 days. Overall, EXACT participants lost one device for every 190 days of observation and answered 78% of random-prompts, a response rate comparable to other EMA studies performed using similar technologies in varied settings [90, 93]

Ecological momentary assessment methods were used to collect data on participant's drug using behaviors. This method employs hand-held devices (Personal digital assistants or mobile phones) that delivered four prompts to complete surveys at random times daily between 8am and 9pm (known as random-prompt entries), and one end-of-day (around 9 pm) survey for 30 days of observation. Participants were also asked to self-initiate a survey and self-report each time they either craved (but refrained from using) or used heroin or cocaine

(or both) in any manner (smoked, snorted or injected); these responses represent event-contingent entries. Heroin only and cocaine only reports incorporated all reports of heroin or cocaine use (including those jointly with another drug). For each event, participants answered questions concerning their drug use, current mood, social, physical and activity environment, using survey instruments adapted from previous EMA studies [89, 90, 95, 100, 101]. Participants had 30 minutes to complete an event-contingent survey to ensure responses were recorded in real-time. *PharmCheck*® Drugs of Abuse Patches (PharmChem Inc.) were collected weekly for the assessment of heroin or cocaine use and at the conclusion of each study week, participants returned to the study site to answer an ACASI that included questions concerning activities, behavior and drug use frequency during the prior week. All data used in the present analyses are from event-contingent entries.

Specific aims

Accordingly, the specific aims of this dissertation are:

AIM 1: To evaluate the concordance of ecological momentary assessment (EMA) methods of drug use to previously validated biological and audio-computer assisted self-interview (ACASI) methods among persons who inject drugs (PWID).

The assessment of illicit drug use via EMA methods has not been previously examined. To do this, EMA methods must be examined in relation to other already known valid and reliable assessment methods including biological sweat samples and self-reports via ACASI interviews. (Chapter 2)

AIM 2: To develop ‘drug using profiles’ collected through Ecological Momentary Assessment (EMA) methods and determine whether these risk profiles are associated with engagement in care.

Unique characterization of drug use at the individual level will enable providers to have a better understanding of a patient’s expectant success of appropriately engaging in care. (Chapter 3)

AIM 3: To examine the real-time social, physical, environmental and psychosocial cues of using versus craving drugs among a sample of drug users utilizing Ecological Momentary Assessment (EMA) methods.

Improving drug treatment outcomes and preventing HIV infection among this high-risk population requires preventing drug relapse. Using ecological

momentary assessment methods, we hope to improve our understanding of the proximate environmental factors of drug use relative to drug craving. (Chapter 4)

Figure 1.1 describes the time intervals of drug use assessments for these analyses. Weekly, daily and real-time intervals for the assessment of drug use were examined through the use of EMA, ACASI and sweat patch methodologies. The use of real-time mHealth methods allows for the assessment of drug use in more refined time intervals and will provide a better understand of varying periods of intense and intermittent drug use and capture the proximate context of the drug using experience.

Overall, this systematic characterization of drug use will allow for more accurate prediction of the triggers of drug use or relapse and can inform development of interventions to improve HIV and drug treatment outcomes.

Conceptual framework

The Information-Motivation-Behavior (IMB) model of adherence suggests adherence information, motivation and behavioral skills interact to determine engagement in care and adherence behaviors [102]. Informed patients include those who are aware they are in need of care as well as the obstacles and barriers to receiving care, including the environments that promote drug craving versus drug use. Motivated individuals include those who have positive attitudes concerning preventing drug relapse and engaging in care, have adequate social support and understand the consequences of non-adherence to care. If an individual is informed and motivated, according to the IMB theory, they will enact adherence related “behavioral skills” such as self-cueing and self-initiation of reducing risky drug-using behaviors and engaging in care, which will result in adherence-related behaviors [102].

It is these behaviors that result in favorable drug treatment outcomes, reductions in drug relapse and positive HIV treatment outcomes such as viral load suppression. The IMB theoretical framework suggests well-informed, well-motivated patients who possess adequate skills for enacting complex patterns of adherence-related behaviors will be less likely to relapse and reduce risky behaviors over time. Yet, even patients who are well informed may or may not be capable of self-motivation or lack the correct behavior skills to comply with treatment due to life

circumstances, such as injecting drugs, co-morbidities such as depression, unstable housing or limited access to care.

The proposed conceptual framework (Figure 1.2) contextualizes the IMB model through consideration of sociodemographics, drug use duration, manner and amount used per day as well as whom the individual was with while using drugs: friend, acquaintance, family member, a stranger, a spouse, and a child, alone, someone currently using drugs (Social Environment), what activity was the participant engaged in when they decided to use: socializing, sleeping, eating, shopping, planning/thinking, drinking alcohol, using tobacco, offered drugs, saw or were with someone using drugs, saw drug paraphernalia, handling \$10 in cash (Activity Environment), where were they when they decided to use: home, another's home, car, bus or train, outdoors, church, job/working, restaurant, abandoned space (Physical Environment) and what was the participant's mood or motivation when using: happy, stressed, tired, relaxed, bored, irritated (Psychosocial Environment (Figure 1.2)). "Situatenedness" in this model allows for the recognition that patient behavior is occurring within a specific cultural, organizational, and structural environment and that outcomes are fundamentally linked to situational and individual factors that may affect drug-using behaviors [103].

We hypothesize that by including social, activity, psychosocial and physical environmental factors collected in real-time into the characterization of drug use, we can better understand drug use and drug craving and the subsequent outcomes associated with these events among chronic drug users. Real-time mHealth methods, such as ecological momentary assessment, will allow for a rich characterization of the drug-using environment beyond the examination of adherence behaviors alone. We also hope to provide evidence for the use of EMA methods to efficiently and effectively collect high quality epidemiological data among a traditionally known hard to reach population.

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Figure 1.1: Time intervals of drug use assessment of proposed work

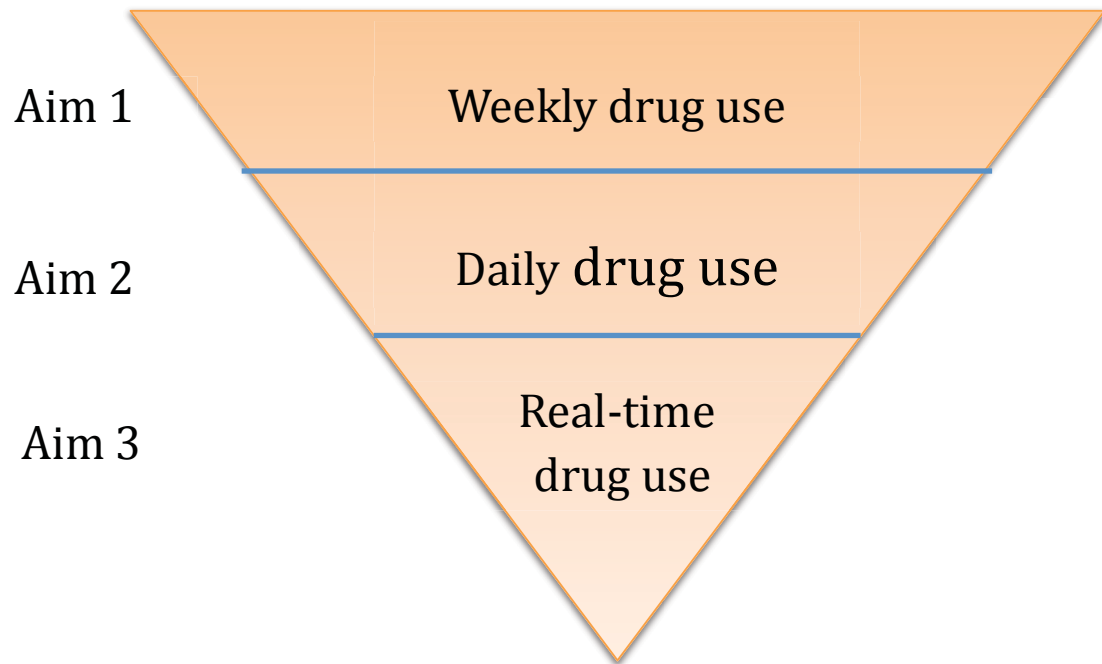
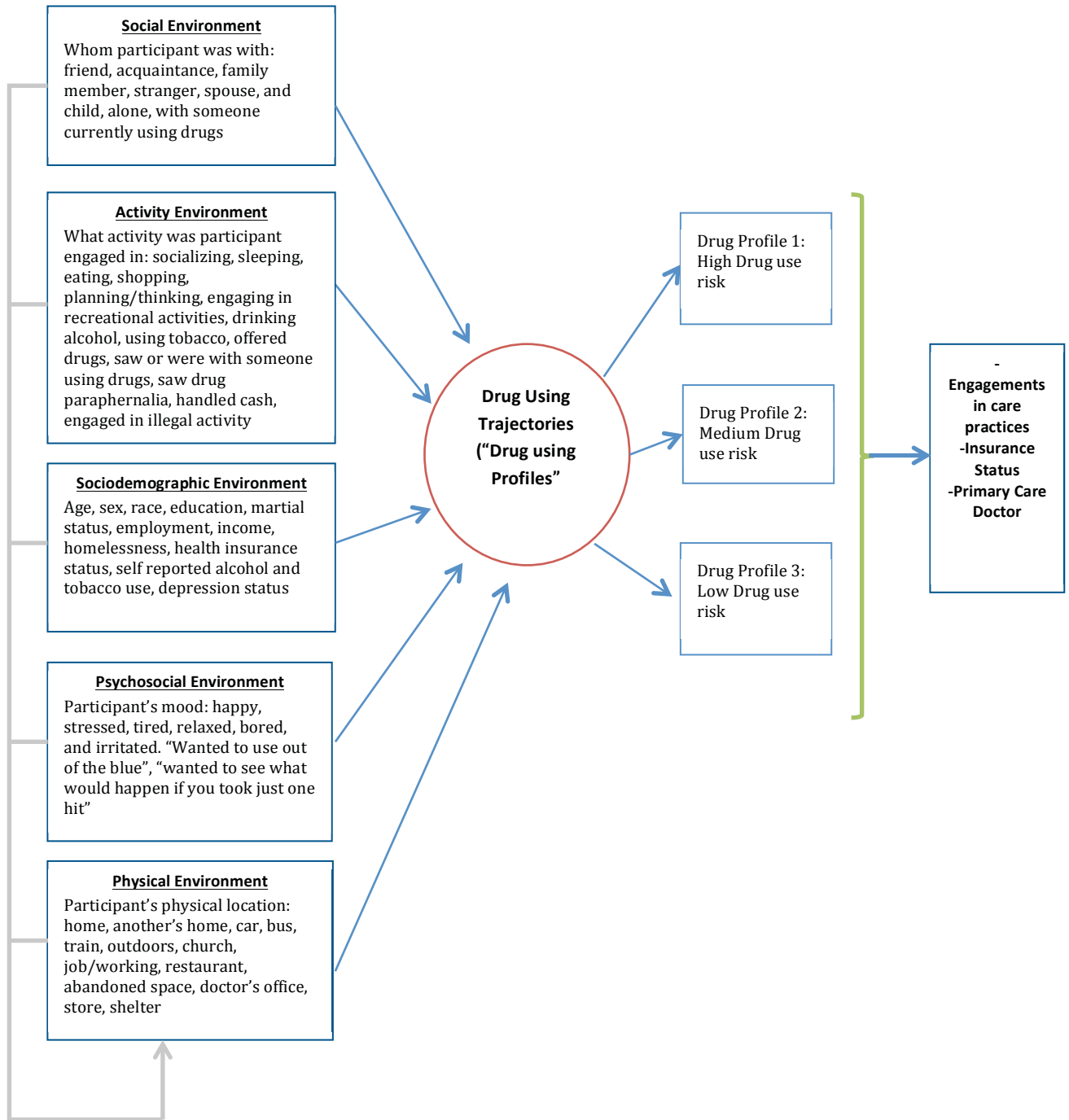


Figure 1.2: Conceptual frame work of proposed work



Chapter 2:

Ecological momentary assessment of illicit drug use compared to biological and self-reported methods

Abstract

Objective: We examined the concordance of ecological momentary assessment (EMA) methods of drug use to previously validated biological and audio-computer assisted self-interview (ACASI) methods.

Methodology: The Exposure Assessment in Current Time (EXACT) study utilized EMA methods to assess drug use in real-time in participants' natural environments. Participants were provided mobile devices and asked to self-report every time they used heroin or cocaine over a 4-week period. At the end of each week, weekly *PharmCheck*® sweat patch samples were collected for measurement of illicit substances. Similarly, participants answered an ACASI-based questionnaire to report activities, behavior and drug using events during the prior week. Reports of cocaine and heroin use captured through EMA methods were compared to weekly biological or self-report measures through percent agreement and kappa statistics. Correlates of discordance were obtained from logistic regression models.

Results: 109 participants were a median of 48.5 years old, 90% African American, 52% male and 59% HIV-infected. In analysis of 424 person-weeks of observation, 212 (50%) cocaine and 103 (25%) heroin sweat patches, 192 (45%) and 161 (38%) ACASI surveys and 163 (38%) and 145 (45%) EMA reports of any cocaine and heroin use were captured over follow-up. The percent agreement

between EMA and sweat patch methods was 70% for cocaine use and 72% for heroin use, while the percent agreement between EMA and ACASI methods was 77% for cocaine and 79% for heroin use. Misreporting of drug use by EMA methods compared to sweat patch and ACASI methods were different by illicit drug type and reflected both the limitations of the assessment methods as well as our sample of more intense high-risk drug users.

Conclusions: Our work demonstrates moderate agreement of EMA methods to biological and standard self-report methods in capturing illicit drug use. Limitations occur with each method and accuracy may differ by type of illicit drugs used.

Introduction

The detection of biochemical markers of illicit drugs in biological samples of hair, urine, sweat or blood is considered the gold standard for assessing illicit drug use and is widely used in drug treatment and employment drug testing settings [1].

The utility of these methods lies in their ability to detect metabolites of illicit drugs used within a specific window of time that varies depending on the biological specimen. Despite being the gold standard for the assessment of drug use, biological samples are often difficult to collect in the field, may be cost prohibitive and can require greater participant engagement (e.g., frequent urine screens at a treatment facility). Additionally, biologic samples typically only assess whether an individual has previously used drugs rather than quantifying how much of the drug was consumed [2, 3]. Whereas fluid samples tend to assess drug use over relatively short windows of time and hair and nail clippings can detect longer periods of drug use, these approaches fail to detect patterns of drug use, such as bingeing or intermittent use.

In epidemiologic studies, the most feasible method of assessing illicit drug use is self-report, which often collects data over extended periods of recall (e.g., 6 to 12 months or longer) [4-7]. The benefit of self-report via survey methodology includes the ease of use, convenience and low cost as well as allowing for further

assessment of risk factors and correlates of drug use (e.g., frequency of use, needle sharing practices or sexual risk-taking practices). However, whether assessed via study interviewer or audio-computer assisted self-interview (ACASI), these methods may involve substantial recall, response and social desirability biases [8, 9]. Additionally, these methods require participants to return to the clinic or study site at regular intervals, which not only requires participants to have reliable transportation options but also disrupts their daily routines. Despite these potential issues, assessment of illicit drug use through self-report has been shown to be a valid and reliable measure of drug use [2, 10-12].

Both self-report and biological testing methods of capturing drug use lack the ability to assess real-time drug use, will miss varying periods of intense or intermittent drug use, and cannot ascertain the proximate context of an individual's drug using experience [13]. Ecological momentary assessment (EMA) methods collect participant-level data in real time over notably shorter time intervals

Mobile health (mHealth) strategies that employ mobile devices (e.g., smartphones or other hand-held devices) can utilize EMA methods for remote data collection and monitoring as well as health education and intervention mHealth methods hold promise for improving health outcomes, healthcare services and public health research [14]. EMA methods have been utilized in smoking cessation studies [15-

21] and among methadone-maintained outpatient drug users [22-26] but have yet to be validated as reliable methods for assessing drug use. By capturing drug-using events in real-time, outside of the study clinic and in participant's natural settings, a more robust, vibrant and comprehensible understanding of drug use can be generated beyond periodic biological detection or infrequent self-reports of drug use.

Prior studies have examined concordance between the assessment of drug use by biological measures and self-report [27-29]. The aim of the current study was to investigate the concordance of assessing drug use via EMA methods compared to biological and ACASI methods. We additionally identified correlates of discordance and examined the feasibility, strengths, and weaknesses of these methods in assessing drug use among a community sample of drug users in Baltimore, MD.

Methods

EXACT study participants

Exposure Assessment in Current Time (EXACT) study participants were recruited from the AIDS Linked to the IntraVenous Experience (ALIVE) study, an ongoing, community-recruited, observational cohort of persons with a history of injecting drugs in Baltimore, MD [7]. The ALIVE cohort is community- rather

than clinic-based, thereby avoiding selection bias toward persons seeking or accessing care. Details of the EXACT study have been previously described [30], and included four successive trials conducted from November 2008 through May 2013. Each trial was planned to follow 30 participants each for 30 days. The Johns Hopkins School of Public Health Institutional Review Board approved the study protocol. All participants provided written informed consent. Participants were informed that involvement (or non-involvement) in EXACT would in no way affect their participation in ALIVE.

Eligibility criteria for the EXACT study included current enrollment in ALIVE and the ability to understand and follow directions on a personal digital assistant (PDA) or mobile phone. Individuals were excluded if they had any medical conditions that would prevent them from operating the hand-held device (e.g., vision or hearing impairment) or failed to attend the screening appointment where they were trained on device use.

In each trial, the specific inclusion criteria regarding drug use and HIV status were varied slightly to ensure a diverse overall sample; both injection and non-injection drug users were included. In Trial 1, selection was made to balance the numbers of participants that reported heroin or cocaine use within the past month (defined as recent drug use) with those that were not currently using drugs. In Trial 2, all participants reported heroin or cocaine use within the prior three months. While

HIV status was not a recruitment criterion in the first two trials, Trial 3 included only HIV-infected participants with recent heroin and cocaine use. These same criteria were also used in Trial 4, but the data collection was transitioned from a PDA to a smartphone platform [30].

For Trials 1-3, participants were provided personal digital assistants (PDA, Palm Z22, Palm, Inc., Sunnyvale, CA, USA) running applications developed using Satellite Forms software (<http://patches.satelliteforms.net/>). All PDA programs were disabled except for study-required applications. In Trial 4, participants were provided an Android Smartphone (Motorola Droid X2), running an application developed using the Electronic Mobile Open-source Comprehensive Health Application (*eMOCHA*) platform, created at Johns Hopkins School of Medicine.

EMA Data Collection

For 30 days of observation, participants were asked to self-initiate a survey on their hand-held device to self-report each time they either used heroin or cocaine (or both) in any manner (smoked, snorted or injected). For each event, participants answered questions concerning their drug use, current mood, social, physical and activity environment, using survey instruments adapted from previous EMA studies [22-26]. To ensure responses were recorded in real-time, participants were required to indicate that drug use had occurred within 30 minutes of

completing this survey. The device also delivered an end-of-day (around 9 pm) survey that asked if there was any drug use that was not reported earlier in the day.

Sweat Patches

PharmCheck® Drugs of Abuse Patches (PharmChem Inc.) were collected weekly for the assessment of heroin or cocaine use. These patches can detect traces of cocaine or heroin secreted in sweat during the period it is worn. Additionally, sweat patches reduce the number of participant visits to the study site thereby reducing any biases associated with missed visits due to drug use. Drugs captured via *PharmCheck*® Sweat Patches represent ‘parent’ drugs (same chemical compound that was taken by the drug user) and drug metabolites (breakdown products of the parent drug) excreted through sweat. The patch can be worn up to 10 days and is able to capture any drug use that occurred during the period of wear as well as 24 hours prior to patch application [31]. To ensure the patch stayed in place, an additional overlay made of the same adhesive material was worn atop the sweat patch. Once removed, patches were sent to a commercial laboratory for drug evaluation (Clinical Reference Laboratory, Lenexa, KS). Specimens were initially screened using an enzyme immunoassay technique (ELISA) with positive patches undergoing confirmation using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS)[31].

Cocaine predominates in sweat after cocaine use, however the most common

metabolite of cocaine is benzoylecgonine (BZ). A positive sweat patch result for cocaine use is confirmed by the presence of both BZ and cocaine at or above the limit of detection of 10ng/mg. Topical analgesics, such as lidocaine or novocain, contain BZ and are used in various surgical procedures, however cocaine is structurally unique and does not resemble any of these products [31].

Opiate metabolites detectable by sweat patch include heroin, 6-monoacetylmorphine (6-MAM), codeine and morphine. The presence of 6-MAM can only come from the use of heroin. A positive sweat patch for heroin includes the presence of the parent drug (heroin) and morphine above the limit of detection of 10ng/ml, 6-MAM and morphine above the limit of detection of 10ng/ml or 6-MAM alone above the limit of detection of 10ng/ml. The presence of morphine alone may be due to the use of other opiate containing legal medications (e.g. oxycodone, hydrocodone) or the consumption of certain foods, like poppy seeds. Therefore, the presence of morphine alone does not indicate a positive sweat patch for heroin [31].

Self-report by ACASI

At the conclusion of each study week, participants returned to the study site to answer an ACASI that included questions concerning activities, behavior and drug use frequency during the prior week. Additionally, baseline participant characteristics were obtained from ACASI completed at enrollment into EXACT

and/or from the prior ALIVE study visit. In addition to sociodemographic variables (e.g., age, sex, race, education, marital status, employment, income, homelessness and health insurance status), baseline data collection included self-reported alcohol, tobacco and illicit drug use, an index of drug abuse [Drug Abuse Screening Test (DAST)] and depressive symptoms [Center for Epidemiologic Studies- Depression Scale (CES-D)] in the prior six-months [32]. Clinical characteristics (e.g. HIV/antiretroviral therapy status, CD4 T-cell count, HIV RNA levels and hepatitis B and C status) were obtained from the existing ALIVE database.

Data analysis

To ensure accurate comparisons between each method of capturing drug use, all analyses were assessed by week (this was necessary as the ACASI and sweat patch data were only collected weekly). The day in which the sweat patch was placed on the participants arm and in which the hand-held device was provided represented the start of the study week 1. Seven days later, when the ACASI was completed, marked the end of the week. At this time, the sweat patch was removed and replaced with a new patch and repeated for all 4 weeks of the study. Drug use reported by ACASI and sweat patch indicated use or no use within the prior week.

Real-time heroin or cocaine use, reported via the EMA event-contingent entries or the end-of-day survey were summed by day and week for each participant. For

analysis, an individual was considered to have used drugs if at least one report of drug use (heroin or cocaine use by any manner) was reported in real-time within a given study week. Heroin only and cocaine only reports incorporated all reports of heroin or cocaine use (including those jointly with the other drug).

Because the sweat patch was able to capture drug use that included the 24hrs prior to adhesion, the EMA week was offset by 1 day to ensure concurrent periods of time were evaluated when comparing the methods. There was no adjustment for time for comparisons between EMA and ACASI-assessed drug use.

To examine the concordance of drug use reported by EMA to sweat patch or to ACASI methods, percent agreement and kappa statistics were calculated. The kappa statistic is a measure of the level of agreement (also known as inter-rater reliability) that takes into account the agreement occurring by chance. Kappa values of less than 0.2 are considered poor; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 good; and 0.81-1.00 very good [33].

If the number of EMA events in any week was greater than the number of ACASI or sweat patch responses it was considered EMA over-reporting, while EMA under-reporting was determined if the number of EMA reports were fewer than those reported by sweat patch or ACASI. To determine correlates of discordance between methods of assessing drug use, logistic regression models with

generalized estimating equations (GEE) were examined. GEE methods adjusted for the correlation of repeated measures within each subject over the 4 weeks of follow-up. Variables selected for the final multivariable models were chosen through step-wise logistic regression with inclusion of significant variables (p-value <0.1) from the univariate analyses. Analyses were performed using STATA Statistical Software: Release 12 (College Station, TX: StataCorp LP).

Results

Among 109 EXACT participants contributing 424 weeks of observation (Table 2.1), the median age was 48.5 years (interquartile range (IQR) 43-53 years), 90% were African American, 52% were male and 59% were HIV infected. In the six-months prior to baseline assessment, 23% of participants reported recent methadone treatment and 83% reported smoking cigarettes.

Comparison of methods to capture illicit drug use

Out of a possible 436 weeks of follow-up, 12 weeks did not have evaluable EMA assessments of drug use (weeks where no drug use was reported via EMA), resulting in 424 weeks (97%) of observable data. Over 424 weeks, 396 (93%) sweat patches were returned and 410 (97%) ACASI surveys were completed (14 were incomplete). Twenty-two individuals were unable to return 29 sweat patches (7%) because the patch was damaged or removed prematurely. 12 individuals did not complete 14 (3%) weekly ACASI surveys. Total weeks of drug use obtained

from sweat patch, ACASI, and EMA methods are described in Figure 2.1. Reports of drug use by EMA represent any report in a week and not the number of individuals or the total amount of uses in a week.

Over study follow-up, 212 (50%, green bars) cocaine positive sweat patches, 192 (45%, blue bars) ACASI surveys and 163 (38%, orange bars) weeks of EMA reports of any cocaine use were captured over follow-up. For heroin use, 103 sweat patches (25%), 161(38%) ACASI surveys and 145 (34%) weeks of EMA reports were captured over follow-up. Seventy-seven sweat patches (18%), 117 (28%) ACASI surveys and 96 (23%) weeks of EMA reports captured both cocaine and heroin use. The proportion of sweat patches with heroin and cocaine detected remained stable by study week.

For cocaine use, the overall percent agreement between EMA and sweat patch methods was 70% (Figure 2.1a, blue bars) (Table 2.2) and for EMA and ACASI methods was 77% (Figure 2.1a, green bars). For heroin use, the percent agreement between EMA and sweat patch methods (Figure 2.1b, orange bars) was 72% and for EMA and ACASI methods (Figure 2.1b, yellow bars) was 79%. With heroin or cocaine use, the percent agreement was slightly higher between the EMA and ACASI methods compared to EMA and sweat patch assessments.

Percent agreement does not take into consideration the agreement between two methods solely due to chance. The kappa statistic is a measure of inter-rater reliability that takes into account the agreement occurring by chance. The kappa statistics were slightly lower for comparisons of drug use between EMA and sweat patch methods than observed for EMA and ACASI methods. The kappa statistics for the comparison of EMA and sweat patch methods were in the moderate agreement range for both cocaine 0.51 (0.44-0.60) and heroin 0.48(0.38-0.57) use. The agreement in reports between EMA and ACASI methods for cocaine use was 0.59 (0.51-0.67) and for heroin use was 0.61 (0.53-0.69), with the former representing moderate agreement and the latter representing good agreement.

Misreporting of responses by EMA relative to sweat patch and ACASI methods were assessed for cocaine and heroin separately (Table 2.2). Relative to sweat patch results, under-reporting of drug use by EMA methods was more likely for heroin than cocaine use (19% vs. 9%), but over-reporting by EMA methods was greater for cocaine than heroin use (21% vs. 8%). Misreporting was identified less commonly between EMA and ACASI methods. Compared to ACASI reports, under-reporting by EMA was infrequent and similar for cocaine and heroin use (8% vs. 9%). Over-reporting by EMA relative to ACASI was slightly greater for cocaine than heroin use (15% vs. 13%).

Comparison of methods to quantify illicit drug use

Variations in weekly self-reported drug use intensity by EMA and ACASI assessment methods are described in Figure 2.3. Among persons reporting any cocaine use during the week by the specified method, the median number of self-reports of cocaine use captured by ACASI (Figure 2.3a, blue boxes) was 4 (Interquartile Range [IQR] 2-6) and the median number of cocaine events captured by EMA (Figure 2.3b, red boxes) was 3 (IQR 1-5). Cocaine events reported via ACASI ranged from 1 to 50 in any week. The greatest number of cocaine use events assessed in any week via EMA was 24.

Similarly, the median number of self-reported heroin use events assessed by ACASI (Figure 2.3b, green boxes) was 4 (IQR 2-7) while the median number captured by EMA (Figure 2.3b, orange boxes) was 2 (IQR 1-4). The greatest number of heroin uses captured by ACASI in any one week was 64 while the greatest number of heroin uses in any week captured by EMA was 38. End of day reports did not substantially impact the daily amount of reported drug use nor did they substantially change the classification of drug use weeks by EMA (data not shown).

Correlates of EMA misreporting

We sought to identify sociodemographic, behavioral or clinical factors associated with over- or under-reporting of drug use by EMA. In multivariable analyses,

relative to sweat patch results, there were no significant correlates of EMA over-reporting of cocaine use (Table 2.3A). Under-reports of cocaine use by EMA were almost 2-fold less likely among females (Adjusted Odds Ratio [aOR] 0.47, 95% Confidence Interval [CI]: 0.23-0.98) and 80% less likely among individuals who reported injecting once per day or more at baseline (aOR 0.21, 95%CI: 0.05-0.87). Although only marginally significant, individuals under 50 years of age were found to be less likely to under-report cocaine use as well (aOR 0.51, 95% CI: 0.25-1.07).

EMA over-reports of heroin use relative to sweat patches were twice as likely if heroin was used (self-reported) at baseline (aOR 2.10, 95% CI: 1.0-4.56), but baseline heroin use was also the only factor significantly associated with EMA under-reporting of heroin use (aOR 5.56, 95% CI: 1.37-22.46). Female gender also achieved marginal significance in being less likely to under-report heroin use via EMA methods (aOR 0.31, 95%CI: 0.08-1.10).

Compared to ACASI methods (Table 2.3B), EMA over-reports of cocaine and heroin use were twice as likely if a participant reported sharing injection needles at baseline (aOR cocaine 2.79, 95% CI: 1.03-7.5; aOR heroin 2.96, 95% CI: 1.17-7.51). Under-reporting of cocaine use by EMA was marginally associated with being married and was 6-fold more likely if individuals reported having medical insurance at baseline (aOR 6.62, 95% I: 1.16-37.76). EMA over-reports of heroin

use were positively associated with baseline heroin use (aOR 3.04, 95% CI: 1.33-6.95) as well as over 4-fold more likely if the participant was HIV infected (aOR 4.56, 95% CI: 1.80-11.58).

Discussion

This analysis demonstrated moderate to strong concordance and inter-rater reliability of reported drug use by EMA when compared to either biological measures of sweat patches or more conventional ACASI self-report methods. However, our data raised concerns regarding the use of sweat patches as a gold standard for drug use assessment due to the notably lower prevalence of heroin use defined by biological detection compared to the prevalence of heroin use we determined in this study based on self-reported methods and to the expected prevalence based on prior data in our ALIVE cohort [7, 34]. Even relative to imperfect gold standards, we provide evidence that researchers should be confident that EMA methods can accurately capture and characterize illicit drug use comparable to currently used methods. Given the relative benefits of daily real-time assessments of drug use in terms of reductions in recall bias, social desirability bias, participant burden and follow-up time, EMA methods for assessing drug use may have broad applications in settings ranging from epidemiological studies to behavioral interventions.

EMA Compared to Sweat Patch Assessment

Biological samples serve as the gold standard for assessing drug use because they are able to capture the biochemical components of drug use as the body excretes them. Sweat patches are often used to detect longer-term drug use as the patch can be worn continuously for up to 10 days and can continuously capture drug metabolites as they break down in sweat until the patch is removed. The patch is designed to be flexible, waterproof and safe from environmental contaminants [35]. The patch can be easily removed, but once the patch comes off the skin, it cannot be put back on to resume drug use capture. Current applications of sweat patch testing include use in drug treatment for monitoring drug relapse and for determining the effectiveness of medical and psychological therapy [36, 37].

Our results suggest moderate concordance between EMA and sweat patch methods for assessing drug use. Prior studies have shown substantial discordance between self-report of drug use and biochemical tests results across out-of-treatment populations [38]. A 10-week outpatient clinical trial in which participants wore sweat patches, provided urine samples and self-reports of cocaine use thrice weekly, demonstrated the concurrent validity of urine and sweat patches to be reasonable (correlation: 0.76, $p < 0.001$), but the correlation between self-report and the patches was lower (correlation: 0.40, $p < 0.05$) [39]. A separate outpatient study examining the utility of sweat testing for monitoring drug use also

found the level of agreement between positive sweat test results and positive urine results to be 33% for heroin and 92% for cocaine [37].

The results of our sweat patch analyses demonstrated a notably greater number of cocaine positive sweat patches compared to heroin positive sweat patches. This finding was unexpected as our prior analyses with this EXACT population demonstrated heroin to be the predominate drug of use over 30 days of follow-up [30]. Additionally, recent estimates indicate that Baltimore suffers from a far greater public health burden of heroin abuse compared to cocaine use [40] and this is mirrored in the participants of the ALIVE study [7, 34]. Upon consultation with *PharmChek*®, manufacturers of the sweat patches, it was suggested this difference may have been the result of our heroin using participants using such small amounts of heroin, that even after a week of wearing the patch, did not secrete enough heroin metabolites to be detected at the limit of detection of 10 ng/ml (Matthew Hartley, personal communication).

A recent study using *PharmChek*® sweat patches examined the stability of 16 drugs at ambient temperatures and reported the degradation of heroin with high individual variability although this effect was not observed with cocaine [41]. We stored our sweat patches at room temp in compliance with *PharmChek*® protocols but have no way of knowing if any of our patches that tested negative, or were below the limit of detection for heroin, were false negatives as a result of possible

degradation. Importantly, despite sweat patches from each week of the study being sent in batch for testing when the participant completed the trial, we did not observe any temporal differences in heroin detection by study week.

Although concerns have been raised that sweat patches may serve as a deterrent to drug use [31], there was no incentive in this study to modify behavior and our self-reported drug use data indicate greater heroin use. To explain our findings, there would have to be a differential effect resulting in heroin misreporting relative to cocaine in response to sweat patch placement, which seems implausible. Yet, despite these problems of relatively lower heroin detection via sweat patches, the inter-rater reliability of EMA methods compared to sweat patch analysis remained moderate for both heroin and cocaine use as evidenced by kappa statistics.

EMA Compared to ACASI Assessment

ACASI methods have now become the standard approach for collecting sensitive data in epidemiologic research studies. The use of ACASI has resulted in greater disclosure of sensitive behaviors such as drug and sexual risky behaviors [42-44], thereby reducing social desirability bias and improving accuracy of self-report.

Although the best time interval for assessing drug use exposure remains unknown, several studies have found that reporting sensitive sexual behaviors can be accurately recalled for intervals of 1–3 months [45, 46]. Longer time frames may be more representative of a person's behavior patterns, but can be more difficult to

recall. It is likely that participants asked to recall behaviors over longer time periods may rely on a strategy such as “guestimation” of the average number of days per week they have been with a specific partner or used drugs [47]. Despite the potential problems with accuracy of information collected over longer periods of time, ACASI assessments are rarely done in shorter intervals due to practical issues.

In this analysis, the inter-rater reliability and concordance of EMA methods compared to ACASI methods for assessing drug use appear stronger for heroin use (kappa statistic for heroin use had good agreement, 0.61[0.53-0.69]) than for cocaine use. Both methods involve self-report in settings with increased privacy over traditional face-to-face interviews providing greater anonymity when disclosing sensitive information. In the current analysis, the ACASI reports captured more drug use than EMA methods. It is hard to differentiate between “fuzzy” recall that may have been reported via ACASI (leading to over-reports) from participants that may have nodded off when answering the EMA survey (leading to under-reports).

While we document good concordance between EMA methods with both ACASI and sweat patch approaches, this analysis neglects to consider a primary analytical strength of EMA methodology, namely the examination of real-time drug use. EMA methods allow for the examination of the variation and amount of drug use

by day. ACASI methods are unable to drill down to daily drug using patterns due to feasibility issues (study visits, etc.). Despite these differences in methodologies, our EMA results remained reliable when compared to ACASI based methods and could prove extremely useful in understanding drug use among community dwelling, non-treatment seeking chronic drug users.

Misreporting by EMA

Relative to sweat patch reports, there were no demographic or behavioral correlates of over-reporting of cocaine use by EMA whereas having a stable partner, male gender and daily injection at baseline were associated with under-reporting of cocaine use by EMA. Baseline heroin use was the only significant correlate of misreporting of heroin by EMA relative to the sweat patch. In total, these data suggest that more regular heroin users were more likely to both over- and under-report heroin, raising concerns regarding misclassification due to the limitations of sweat patch detection of heroin as highlighted above.

Relative to ACASI, sharing injection needles was positively associated with EMA over-reporting of both cocaine and heroin use, while under-reports of cocaine use was positively associated with having medical insurance. In contrast, EMA under-reporting of heroin use were positively associated with baseline heroin use and HIV status. Stable factors, such as having insurance, may lead to underreporting of cocaine use as a result of a social desirability bias. The associations of

misreporting with sharing needles, baseline heroin use and HIV status most likely reflects the recruitment criteria of EXACT, which included a large proportion of HIV infected individuals with more recent and intense drug use.

Substance abuse is commonly associated with a chaotic or disordered life, mental illness, financial and legal difficulties, and inadequate housing or transportation [48-50]. As members of the ALIVE cohort, all EXACT participants had a history of abusing illicit drugs and most were HIV infected. Long-term chronic drug abuse has physical ramifications but also cognitive effects. Working memory deficits are also prominent among HIV infected individuals. During periods of intoxication, heroin users suffer a slow drop off in attention and often fall asleep [51]. Baseline cocaine and heroin use heavily impacted EMA misreporting of heroin use but not cocaine use. It is possible that inattention or sleep may have contributed to heroin users (more so than cocaine users) difficulties in recalling drug use on a weekly basis (both as over reports and under reports) as was required of drug use assessed by ACASI. With respect to EMA under-reporting, we found no evidence of exhaustion from using the hand-held devices in reporting drug across study week or by drug type. Notwithstanding these differences in reporting by drug type, EMA methods captured much of the drug use reported by ACASI methods.

There are several strengths of EMA methods that make them desirable to capture illicit drug use among community-dwelling populations. Because they are assessed in essentially real-time, EMA does not require individuals to recall or remember behaviors for prolonged periods. Social desirability bias is a reporting bias that arises when individuals under-report specific behaviors or actions because they believe they are sensitive and not socially acceptable to report [52]. ACASI methods have been shown to decrease social desirability bias by allowing greater respondent privacy because questions are administered audibly and in text on a computer screen in a private room without the direct participation of a study interviewer [44]. However, EMA methods may allow for even greater respondent privacy, as participants are able to answer questions in their natural environment, allowing participants to calmly respond to questions where they feel most comfortable, away from a study site. ACASI interviews and sweat patches require participants to visit study sites at regular intervals.

For ACASI assessments, a missed visit may mean a whole year passes before participants report on their behaviors. Missing an EMA prompt does not have the same impact on data collection; participants have multiple opportunities to self-cue and self-report specific behaviors as well as respond to surveys throughout the day, making the impact of missing one reported event less problematic for analyses.

Additionally, EMA methods can provide more intensive follow-up opportunities compared to sweat patch or ACASI assessment. Daily outcome assessments over extended periods of time are feasible when using EMA methods because participants carry the devices 24 hours a day 7 days a week. Prior studies have involved participants using the devices for up to 6-months [25]. Real-time data capture allows for the daily context and “situatedness” of drug use to be assessed, including information on the number of days used, frequency and amount used in a day, as well as participant behaviors that occur due to specific cultural, organizational, and structural environments [13]. Historically, ACASI has resulted in greater disclosure of sensitive information [42-44] and previous EMA analyses by ourselves and others have demonstrated that EMA is capable of capturing this type of information as well [23, 24, 26, 30, 53].

Assessing drug use in epidemiologic studies must involve an approach that is unobtrusive, does not rely on recall, has limited requirements for participant participation, and is accessible and affordable. mHealth may provide an excellent solution for assessing drug use in the field. Beyond real-time self-reporting, mHealth strategies may include remote monitoring with wearable sensors which are currently under evaluation to identify the onset and duration of cocaine use. iMStrong (PI Edward Boyer, Univ of Massachusetts Med Sch) is a system comprised of an unobtrusive, wearable sensors that continuously record and wirelessly transmit physiologic measures (e.g., increased electrodermal activity,

skin temperature, and motion) of sympathetic nervous system arousal that works with a smartphone to alert individuals to the onset of drug cravings. “AutoSense” uses a wearable sensor that can collect heart rate, respiration patterns and blood alcohol levels in a person’s natural environment [54]. These early prototype methods for real-time quantification of illicit drug use will likely evolve to become more reliable and proficient, expand accessibility, and be adaptable for measuring multiple substances concurrently.

The level of concordance between EMA and traditional biological and self-report methods suggests that utilizing EMA mHealth strategies are feasible for assessing drug use among community dwelling, non-treatment seeking drug users. Future studies integrating EMA methods with the use of sensors for assessing drug use will likely provide both the biological and environmental cues of illicit drug use as well as provide a more complete picture of drug using behaviors.

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Table 2.1: Baseline characteristics of EXACT participants *

Characteristic	All Trials (N=109)
Sociodemographic Variables	N (%)
Median age, years (IQR)	48.5 (43.3-52.9)
African American	98(90)
Male	58 (52)
High school education	44 (41)
Never married	66 (61)
Income, yearly < \$5000	83 (78)
Medical insurance	93 (85)
Homeless	9(8)
Have primary care doctor	97 (89)
Emergency room visit (ER)	28(26)
Substance Use Variables	
Cigarette use	91 (83)
Alcohol use	71 (65)
Marijuana use	27 (25)
Cocaine use (any route)	54 (47)
Heroin use (any route)	52 (46)
Speedball	26 (23)
Drug Abuse Screening Test, DAST>16	
Clinical Variables	
Depressive symptoms (CESD >23)	26 (23)
Methadone treatment	26 (23)
Hepatitis C virus seropositive	94 (86)
HIV positive †	64 (59)
Median CD4 (IQR)†	360.5 (239-529)
HIV viral load > 500 copies/mL †	35 (55)
Any retroviral therapy	42(65)

* All baseline characteristics represent behavior within the 6 months prior to the start of EXACT

†HIV+ status was an inclusion criterion for Trials 3 & 4; CD4 & viral load tested on HIV-positive participants only.

Figure 2.1: Reported drug use by ACASI, EMA and sweat patch methods

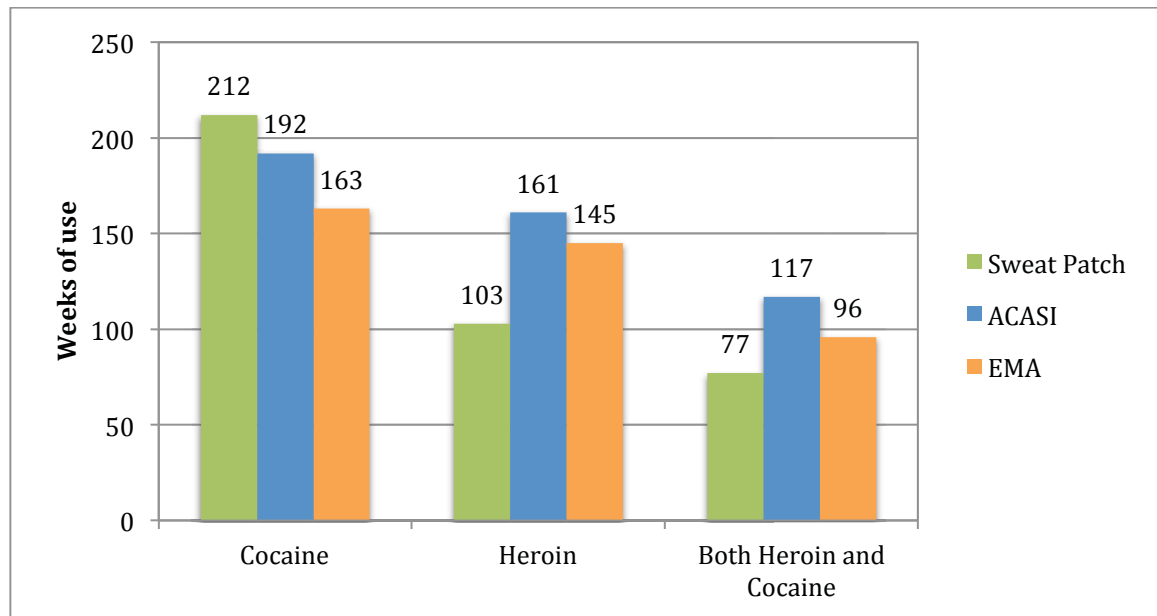


Figure 2.1. Counts of weeks of reported drug use as assessed by sweat patch (green bars), EMA (orange bars) or ACASI (blue bars) method

Figure 2.2: Percent agreement by drug type and week comparing EMA, sweat patch and ACASI methods

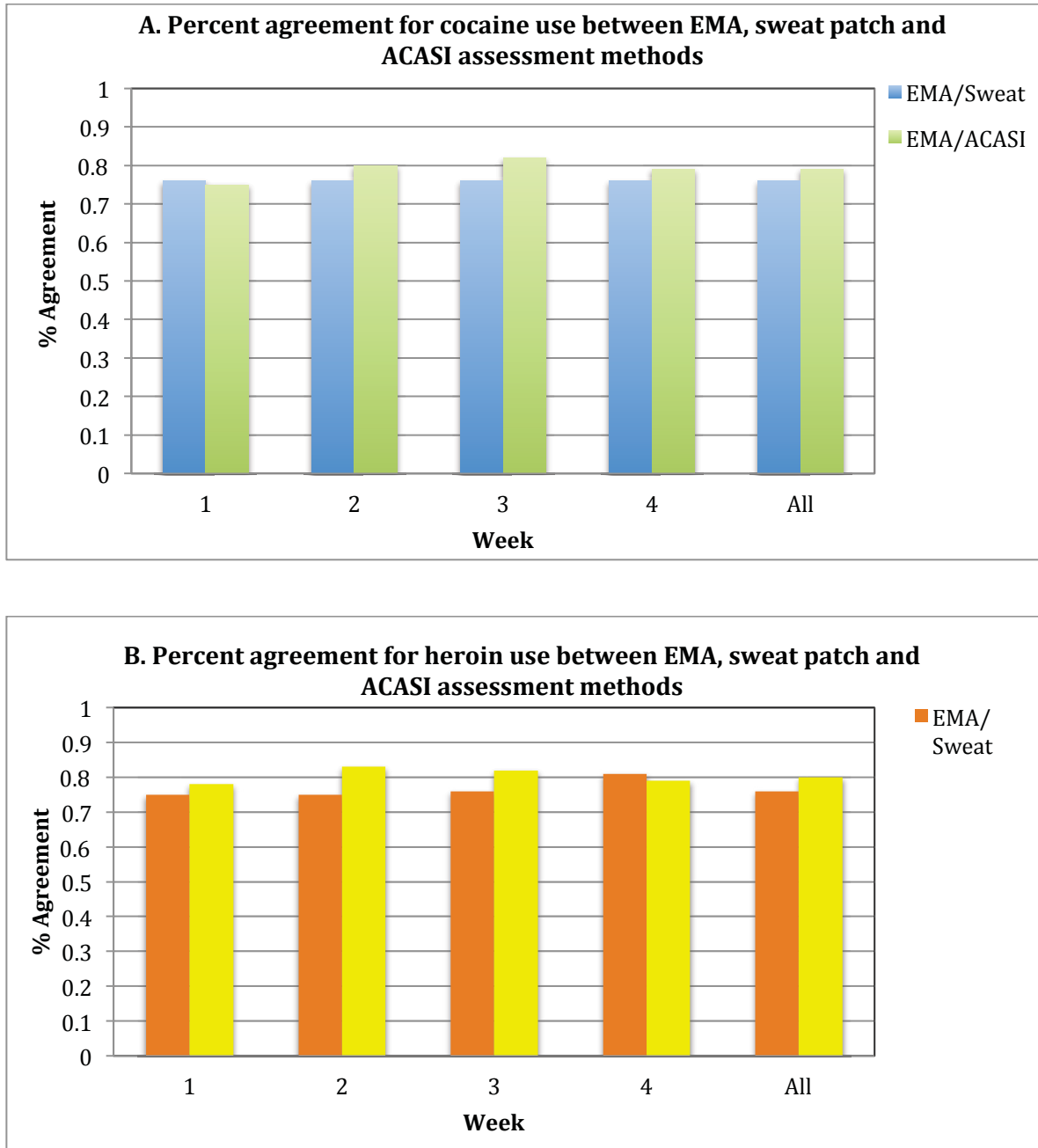


Figure 2.2. Percent agreement by drug type and week comparing EMA, sweat patch and ACASI methods. Panel A: Percent agreement between EMA/Sweat Patch methods (blue bars) and EMA/ACASI methods (green bars) by week for cocaine use. Panel B: Percent agreement between EMA/Sweat Patch methods (orange bars) and EMA/ACASI methods (grey bars) by week for heroin use.

Table 2.2: Percent agreement, over and underreporting of EMA responses compared to sweat patch and ACASI response by drug type

	Cocaine		Heroin	
	N	%	N	%
Reported yes on EMA/sweat patch negative (Over report)	30	9%	70	19%
EMA & Sweat Patch concordant	298	70%	307	72%
Reported no on EMA/sweat patch positive (Underreport)	79	21%	28	8%
Reported yes on EMA/ACASI negative (Over report)	29	8%	33	9%
EMA & ACASI concordant	327	77%	335	79%
Reported no on EMA/ACASI positive (Underreport)	58	15%	49	13%

Figure 2.3: Frequency of cocaine (A) and heroin (B) use by week as reported by EMA and ACASI methods

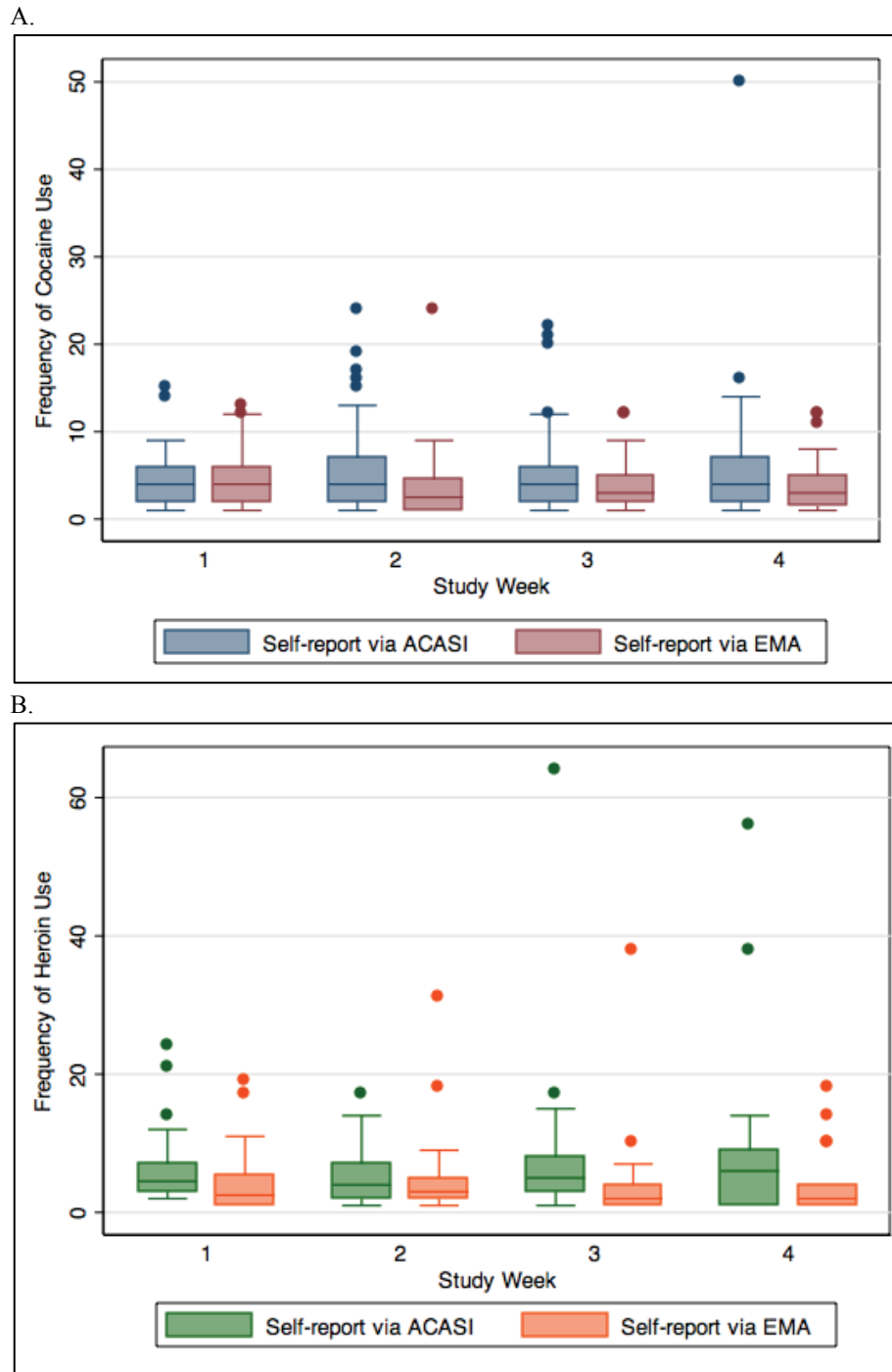


Figure 2.3. Frequency of cocaine and heroin use by study week as reported by EMA and ACASI methods. Plot A: Box plots of the median, 25th and 75th percentiles of self-reported frequencies of cocaine use by week as assessed by ACASI (blue boxes) and EMA (red boxes) methods. Plot B: Box plots of the median, 25th and 75th percentiles of self-reported frequencies of heroin use by week as assessed by ACASI (green boxes) and EMA (orange boxes) methods.

Table 2.3: Correlates of misreporting cocaine and heroin by EMA compared to sweat patch (A) or ACASI (B) methods*

A. EMA/Sweat patch	Cocaine EMA Over-report	Cocaine EMA Under-report	Heroin EMA Over-Report	Heroin EMA Under-Report
	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Female		0.47 (0.23-.98)		<i>0.31(0.08-1.1)</i> ⁺
Age≥50			0.52(0.24-1.14)	
Never Married		<i>0.51(0.25-1.07)</i> ⁺		0.68(0.21-2.19)
Alcohol Use		1.55(0.72-3.36)		
Insurance		3.15(0.76-13.05)		
Any heroin			2.10(1.0-4.56)	5.56 (1.37-22.46)
Any cocaine		1.55(0.72-3.36)	1.68(0.79-3.62)	
Same doctor for at least 2 years			0.60(0.30-1.23)	
Inject≥1/day		0.21(0.05- 0.87)		

B. EMA/ACASI	Cocaine EMA Over-report	Cocaine EMA Under-report	Heroin EMA Over-Report	Heroin EMA Under-Report
	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Age≥50			<i>0.42(0.17-1.07)</i> ⁺	
Never Married		<i>0.47(0.21-1.02)</i> ⁺		0.53(0.24-1.18)
Cigarette use		2.73(0.64-11.72)	2.88(0.61-13.57)	2.76(0.46-16.55)
Alcohol use		1.73(0.69-4.29)		
Insurance		6.62(1.16-37.76)		
Any heroin			0.77(0.29-1.99)	3.04(1.33-6.95)
Any cocaine		1.78(0.76-4.20)	1.86(0.77-4.51)	1.19(0.53-2.68)
HIV infected	0.52(0.18-1.5)			4.56(1.80-11.58)
Shared needles	2.79(1.03-7.5)		2.96(1.17-7.51)	
Primary care physician	0.57(0.15-2.14)			
Yearly income<\$5,000			1.69(0.45-6.34)	

* Correlates included in multivariable models had p-values<0.1 in univariate analyses and represent behaviors occurring within the 6 months prior to the start of EXACT

Bold values indicate statistical significance, p-value<0.05

⁺Italic values indicate marginal statistical significance, p-value<0.1

Chapter 3:

Utilizing mHealth to Identify Illicit Drug Users at Risk for Poor Engagement in Care

Abstract

Background: We examined whether mobile health (mHealth) methods of collecting data in real-time could effectively identify drug users with high-risk drug use behavior, and whether these high-risk drug users had indicators of poorer engagement in care.

Methodology: Participants from the AIDS Linked to the IntraVenous Experience (ALIVE) study in Baltimore, MD were recruited into the EXposure Assessment in Current Time (EXACT) study. Participants were given a mobile device for assessment of their daily drug use (heroin, cocaine or both), mood and social context for a 4-week period. Real-time, self-reported drug use events were summed for each individual by day and drug use risk was assessed through latent class growth mixture models. Latent class regression examined the association of mHealth-defined risk groups with sociodemographic and clinical characteristics and with indicators of engagement in care.

Results: 109 participants were a median of 48.5 years old, 90% African American, 52% male and 59% HIV-infected. Growth mixture modeling identified three distinct classes: low intensity drug use (25%), moderate intensity drug use (65%) and high intensity drug use (10%). Individuals classified as high intensity users were younger, injected greater than once per day and shared needles, relative

to the low intensity drug using class. At the subsequent ALIVE visit, individuals classified as high intensity drug users were nine times less likely to be medically insured (adjusted OR: 0.10, 95%CI: 0.01-0.88) and were at greater risk for failing to attend any outpatient appointments (aOR: 0.13, 95%CI: 0.02-0.85) relative to low intensity drug users.

Conclusions: Real-time collection of drug use EMA data using mobile devices identified a distinct class of drug users with high-risk behavior at risk for poor engagement in care. mHealth monitoring holds promise for identifying high-risk persons and potentially targeting and efficiently delivering real-time interventions to improve drug treatment and HIV care outcomes.

Introduction

Optimal engagement in HIV care is characterized by swift linkage and enrollment after diagnosis, prolonged retention in care, and sustained adherence to prescribed antiretroviral therapy (ART) regimens [1]. Individuals with substance abuse problems tend to have a range of vulnerabilities that increase their risk of both becoming HIV infected and failing to achieve the desired treatment outcome of viral suppression. Regardless of HIV status, engagement in health care entails specific actions that individuals must take to achieve the best outcomes from available health care services [2]; for example, having a primary care physician and regularly attending outpatient appointments rather than utilizing the emergency department for primary care needs(which is exceedingly expensive) .

People who inject drugs (PWID) are often poorly engaged in care due to the multiple contributing factors of prolonged substance abuse, mental health disorders, HIV and hepatitis C virus (HCV) infection, unstable housing, violence, poverty and incarceration [3-5]. Identifying drug users at risk for poor engagement in care could allow for targeted and tailored interventions to foster engagement and prevent needless morbidity and mortality.

In epidemiologic studies, ascertainment of illicit drug use is commonly by self-report, which lends the data susceptible to substantial recall bias, particularly when captured within broad time periods (e.g., “any drug use in the past year”) [4, 6, 7].

Further, details regarding the intensity and patterns of drug use are rarely captured [8, 9]. These recall methods are limited in their ability to identify periods of daily intense or intermittent use and fail to capture the context of an individual's drug using experience.

Ecological Momentary Assessment (EMA) methods are able to collect patient-level data in real time as well as facilitate responsive communication between clinic and patient utilizing smart phones or hand-held devices. These mobile health (mHealth) methods have been utilized in smoking cessation studies [10-15] and in methadone-maintained outpatient drug users to examine activities associated with cocaine and heroin use [11, 16-20]. Detailed, longitudinal EMA data can provide information at varying time intervals (e.g. hourly, daily, weekly) of the changes and patterns of behaviors that are often not static over longer periods of time. By assessing participants in real-time, EMA studies can reduce recall biases and distinguish behavioral nuances that are not captured at periodic study visits every 6 months or yearly as performed in many traditional cohort studies.

For many health-related conditions, long-term assessments (e.g. longitudinal data) are necessary to derive meaningful associations between exposures and outcomes as well as to describe heterogeneous patterns of exposure. Analytic methods, such as growth mixture modeling, have been previously used to identify distinct trajectories of drug using behavior over extended periods of time [21-23] but these

methods have yet to be widely applied to EMA data.

To our knowledge, the current analysis is the first to utilize EMA methods to ascertain 30-day drug-using trajectories among a sample of drug users in Baltimore, MD and to identify sociodemographic and behavioral predictors of these drug-using trajectories. Finally, we evaluated whether EMA-derived drug using trajectories were associated with subsequent indicators of engagement in care.

Methods

EXACT study participants

Exposure Assessment in Current Time (EXACT) study participants were recruited from the AIDS Linked to the IntraVenous Experience (ALIVE) study, an on-going, community-recruited, observational cohort of over 3,000 persons with a history of injecting drugs in Baltimore, MD[24]. The ALIVE cohort is community-based rather than clinic-based, thereby avoiding selection bias toward persons seeking or accessing care. Details of the EXACT study have been previously described [25], and included four successive trials conducted from November 2008 through May 2013. Each trial was planned to follow 30 participants each for 30 days.

Eligibility criteria for EXACT included current enrollment in ALIVE and the ability to understand and follow directions on a personal digital assistant (PDA) or mobile phone. Individuals were excluded if they had any medical conditions that would prevent them from operating the hand held device (e.g., vision or hearing impairment) or failed to attend the screening appointment where they were trained on how to use the device.

In each trial, the specific inclusion criteria regarding drug use and HIV status were varied slightly to ensure a diverse sample and drug use included any route of administration (injection and non-injection). In Trial 1, selection was made to balance the numbers of participants that reported heroin or cocaine use within the past month (defined as recent drug use) with those that were not currently using drugs. In Trial 2, all participants reported heroin or cocaine use within the prior three months. While HIV status was not a recruitment criterion in the first two trials, Trial 3 included only HIV-infected participants with recent heroin and cocaine use. These same criteria were also used in Trial 4, but the data collection was transitioned from a PDA to a smartphone platform [25]. Participants from all trials are included in this analysis.

The Johns Hopkins School of Public Health Institutional Review Board approved the study protocols. All participants in the EXACT study provided written informed consent and were informed that involvement (or

non-involvement) in EXACT would in no way affect their participation in ALIVE.

Data

Hand-held devices delivered four prompts to complete surveys at random times daily between 8am and 9pm (known as random-prompt entries), and one end-of-day (around 9 pm) survey for 30 days of observation. Participants were also asked to self-initiate a survey and self-report each time they either craved (but refrained from using) or used heroin or cocaine (or both) in any manner (smoked, snorted or injected); these responses represent event-contingent entries. Heroin only and cocaine only reports incorporated all reports of heroin or cocaine use respectively, including those when used jointly with another drug.

For each event, participants answered questions concerning their drug use, current mood, social, physical and activity environment, using survey instruments adapted from previous EMA studies [16-20]. To ensure responses to event-contingent surveys were recorded in real-time, participants were required to indicate that the craving or use had occurred within the prior 30 minutes. All data used in the present analyses are from event-contingent entries from all trials.

For Trials 1-3, participants were provided personal digital assistants (PDA, Palm Z22, Palm, Inc., Sunnyvale, CA, USA) running applications developed using

Satellite Forms software (<http://www.satelliteforms.net/>). All PDA programs were disabled except for study-required applications. In Trial 4, participants were provided an Android Smartphone (Motorola Droid X2), running an application developed using the electronic mobile comprehensive health application (emocha), mHealth platform, created at Johns Hopkins School of Medicine. Previously, emocha had been used to support community health workers in resource limited settings heavily impacted by HIV [26] and was modified specifically for this study.

Exposure data were additionally obtained from audio-computer assisted self-interviews (ACASI) completed at enrollment into EXACT or from the existing ALIVE database which includes sociodemographic, behavioral, and clinical data obtained during biannual study visits. In addition to sociodemographic variables (e.g., age, sex, race, education, marital status, employment, income, homelessness and health insurance status), baseline data collection included self-reported alcohol, tobacco and illicit drug use [as assessed by a score ≥ 16 via the 28-item Drug Abuse Screening Test (DAST)], and depressive symptoms [as assessed by a score ≥ 23 via the Center for Epidemiologic Studies- Depression Scale (CES-D)] in the prior 6 months [27].

Statistical Analyses:

The outcome of this analysis was number of self-reported heroin and/or cocaine use events per day over 30 consecutive days. As a first step, we examined the individual patterns of daily drug use overall and by type of drug used. To further characterize heterogeneous patterns of drug use, the data were modeled using semi-parametric latent class growth mixture models [28, 29], specifically the zero-inflated Poisson model (ZIP) since the outcome was a count with an excess of zero totals. This approach was used to classify participants into different groups, each representing different subpopulations with unique longitudinal patterns. Although the number of groups can be hypothesized *a priori*, one aim of this method is to determine the number of meaningful groups that exist in the population. Selecting the number of groups involved fitting a series of iterative models, varying the number of groups up to 4. Models were compared using the Bayesian Information Criterion (BIC), the average posterior probabilities of group membership and the usefulness of the number of groups in practice [30, 31]. Group membership was assigned by maximum posterior probability and groups were labeled based on group characteristics. Backward selection of the parameters representing time (e.g., linear, quadratic, cubic) was used to determine trajectory shapes and parameters were removed on the basis of statistical significance ($P \leq 0.05$).

Baseline sociodemographic and behavioral characteristics were included as time-fixed covariates in bivariate analyses to describe the increase in relative odds of

being in a trajectory group (relative to the lowest risk group) per unit increase in the risk factor. The limited sample size prohibited multivariable analyses.

Logistic regression methods were utilized to examine if EMA classes could predict key indicators of engagement in care at the next ALIVE visit (5 months after EXACT was completed). These outcomes included having any medical insurance or attending outpatient physician visits. Other predictors of engagement in care included baseline sociodemographic and behavioral characteristics.

Analyses were performed using STATA 12 (Stata Statistical Software, College Station, Texas) and SAS 9.2 (Proc Traj; SAS Institute Inc., Cary, North Carolina).

Results

Table 3.1 provides baseline characteristic data for the 109 participants enrolled in EXACT. The median age was 48.5 years (inter-quartile range (IQR): 43-53 years), 90% were African American, 52% male and 59% were infected with HIV. Prior to EXACT, 77% of participants reported earning less than \$5,000 in annual income, 23% of participants reported recent methadone treatment and 23% had substantial depressive symptoms with a score of 23 or above on the CES-D. Almost ninety percent (89%) reported they had a primary care physician at baseline. At study entry, 65% of participants reported recent alcohol consumption and 83% reported smoking cigarettes daily in the prior six-months.

The 109 EXACT participants were followed for a median of 28 days (IQR 26-29), during which time 98 (90%) participants reported using heroin or cocaine (in any manner) at least once while 11 (10%) did not report any drug use. The median number of self-reported craving events was 8 (IQR 5-14) and the median number of self-reported drug using events was 4 (IQR 1-10). Of 844 total drug use events, 351 (41.6%) were exclusively heroin, 289 (34.2%) were exclusively cocaine and 201 (23.8%) were reports of concurrently using both heroin and cocaine.

Figure 3.1 displays lattice plots (also known as heat maps) of the daily intensity of any self-reported drug use (Panel A), heroin use (Panel B) and cocaine use (Panel C) of EXACT participants over the 30 days of follow-up. Only participants reporting drug use were included in these figures (persons with cravings only were excluded). Individuals are represented on the y-axis and the color intensity indicates the intensity of self-reported drug use for any given day (darker colors represent more reports of drug use).

Among individuals self-reporting any drug use (Figure 3.1, Panel A), the mean number of drug-using days during study follow-up was 7.7 (standard deviation [SD] ± 6.7 days), with a range of 1-28 days. Over the 30-day follow-up period, the mean number of drug use events was 11 (SD ± 16); the median number was 6.5 events (IQR 3-13), with a range of 1-105 reports.

Among individuals self-reporting heroin use (Figure 3.1, Panel B) the mean number of heroin-using days over follow-up was 6.6 days (SD \pm 6.5days). Over the 30-day follow-up period, the mean number of heroin use events was 10 (SD \pm 15.1); the median number of heroin use events was 4.5 (IQR 2.0-10.5), and a maximum of 93 heroin use events were reported over follow-up. The greatest number of heroin use events in any one day was 7.

On average, cocaine use was reported on 6.2 days (SD \pm 5.3 days) during follow-up (Figure 3.1, Panel C). Among all participants reporting cocaine use, an average of 8 (SD \pm 9.5) cocaine use events, a median of 4 (IQR 3-10) cocaine use events, and a maximum of 61 cocaine use events were reported over the 30 days of EXACT. The greatest number of cocaine events reported in any one day was 5.

EMA-defined drug using risk groups

Mean drug use per day was examined using semi-parametric growth mixture models with 2, 3, and 4 groups and time modeled linearly. Despite the slightly better fit provided by the 2-group model (as evidenced by the largest negative BIC), the 3-group unadjusted model was chosen as the final model for the observed data (BIC 2-group= -1241.9, BIC 3-group= -1182.8, BIC 4-group= -1162.1) as it defined three interpretable and relevant subgroups with a low BIC. The groups were labeled for convenience based on their profiles of response as: low intensity drug use (Group 1), moderate intensity drug use (Group 2) and high

intensity drug use (multiple uses per day, Group 3). The average probability of most likely group membership was between 0.87 and 0.96 indicating a high degree of classification accuracy and exceeding the threshold of 0.70 suggested for these methods [32].

Figure 3.2 displays the trajectories of drug use over time based on the 3-group model. Although cubic and quadratic fits were explored, all three groups were best fit with linear trajectories. Group 1 represented 25.0% of the participants with a mean of 0 drug use events per day (SD +/- 0.04). The moderate intensity drug-using group (Group 2) comprised approximately 65.0% of participants and was marked by an overall average of less than 1 (SD +/- 0.19) drug use events per day (SD +/-0.19), with a slight decline over the study period. Group 3 represented individuals using drugs multiple times daily (10.5% of participants). This group was marked by an overall average of 1.5 drug use events per day (SD +/- 0.85).

Sociodemographic and behavioral characteristics of drug using risk groups:

Factors associated with membership in the EMA-defined drug-using risk groups were examined by separately comparing Group 2 (moderate intensity users) and Group 3 (high intensity users) to the Group 1 participants with stably low to no reported drug use as the referent group (Table 3.2). Moderate intensity drug users (Group 2) had lower odds of being married (log Odds Ratio (log OR): -1.48, p-value=0.036) and increased odds of being a current injector (log OR injecting

≥ 1 /day: 2.17, p-value=0.049), injecting heroin (log OR: 2.26, p-value=0.007) and using crack (log OR: 2.60, p-value=0.015) relative to Group 1. High intensity drug users (Group 3) were more likely to be younger (log OR: -2.11, p-value=0.068), share needles (log OR: 2.70, p-value=0.0296) and inject cocaine (log OR: 2.34, p-value=0.028), inject heroin (log OR: 3.31, p-value=0.003), use crack (log OR: 3.25, p-value=0.009) and speedball (log OR: 2.70, p-value=0.043) relative to those in Group 1. Additionally, compared to individuals reporting low intensity drug use, high intensity drug users had lower odds of being HIV positive (log OR: -1.94, p-value=0.042).

Associations of drug using risk groups with subsequent engagement in care indicators

We next examined the association of EMA-classified drug using risk groups with subsequent engagement in care outcomes as determined through the ALIVE study follow-up. At the first ALIVE study visit following EXACT study completion, 84% of EXACT participants reported having medical insurance of any kind (private or public) and 72% reported attending an outpatient medical appointment.

In unadjusted analyses (Table 3.3), high intensity drug users (Group 3) were 79% less likely to report attending outpatient appointments relative to low intensity drug users (OR: 0.19; 95% confidence interval [CI], 0.03-1.04). Additionally,

compared to low intensity drug users, high intensity drug users had lower odds of having medical insurance (OR: 0.19; 95% CI, 0.03-1.04)

In adjusted analyses (Table 3.4), the final model for being engaged in care (defined as reporting subsequent outpatient visits and having medical insurance) included drug use intensity groups, being older, female gender, homelessness and recent methadone treatment. Adjusting for these covariates, individuals in the high intensity drug-using group reported an 88% reduced likelihood (aOR 0.12; 95% CI, 0.02-0.85) of reporting outpatient visits relative to low intensity users. Compared to low intensity users, high intensity drug users were also less likely to have medical insurance (aOR 0.10; 95% CI, 0.01-0.88).

Discussion

Our results demonstrated that collecting self-reported drug using data utilizing Ecological Momentary Assessment (EMA) methods allowed for an in-depth understanding of the heterogeneous patterns of drug use and associated behaviors. Growth mixture modeling of real-time reports of daily heroin or cocaine use over a 30 day study period distinguished three drug using risk groups, represented as low, moderate and high intensity drug use. Our analysis demonstrated distinct behavioral profiles for each risk group with the high intensity users comprised of younger, polysubstance users who more likely to share needles but not to be HIV infected. Importantly, during subsequent follow-up the drug using groups we

identified were predictive of indicators of poor engagement in care. These findings provide a richer and more informed understanding of individual trajectories of drug use. Drug-use patterns obtained through mHealth approaches may provide a platform for future development of personalized, context-sensitive interventions (Ecological Momentary Interventions, EMI) for HIV treatment and drug cessation programs.

Studies of HIV-infected drug users often simplistically categorize persons into a broad IDU risk group irrespective of recency, type or intensity of use. All participants of the EXACT Study reported injecting drugs at some point within the prior six months, as they are members of the ALIVE study. Other epidemiologic studies crudely define drug use as “any drug use” during a specified time interval, commonly over the prior 6 months to a year [4, 6, 7]. In drug treatment studies, drug use is often categorized as any use compared to cessation, although measures of drug use intensity are becoming of interest (e.g., number of days used in the past month). This analysis demonstrated the average number of days used in the past month to be approximately 8. None of these methods describe the severity or timing of drug use. Our EMA data provided more refined assessments of drug using behavior, including daily intense or intermittent use. This is what makes EMA data unique, the ability to capture more refined assessments of drug using behavior. As a result, our analyses were able to demonstrate the presence of non-uniformity in drug using risk that varied by sociodemographics, drug type, and

frequency of daily use.

The three drug using risk groups defined in this analysis represent individuals with increasing intensity of heroin or cocaine use. A quarter of study participants were in the low intensity drug-using group as they reported little heroin or cocaine use over the 30-day follow-up. This is an expected finding based on the eligibility criteria which aimed to recruit participants with variable intensities of drug use. Even among our population of self-identified injection drug users, this analysis found a low intensity drug using group, which provided a baseline for comparisons between groups represented by varying intensities of heroin and cocaine use. This also highlights the need for community-based samples as these low intensity users are rarely seen in drug treatment studies.

The moderate intensity drug-using trajectory had the largest membership, was associated with prior injecting heroin and smoking crack relative to the low intensity drug-using group. Despite polyroute drug use, these individuals reported less than daily drug use over follow-up and no behaviors associated with HIV risk including sharing syringes, all of which may represent reduced drug addiction [33, 34]. Interestingly at baseline, injecting more than once a day (not drug specific) was associated with membership in this group. This could be a result of recall bias that is common in cohort studies semi-annual study visits. At the baseline, participants were asked to recall their injection drug using behavior in the prior 6-

months and these behaviors did not uniformly match what participants reported in real-time. This discrepancy in reporting may provide insight into how drug addiction is characterized and quantified. Rather than rely on baseline assessments of injection behaviors, drug type and intensity of use may provide better insight to an individual's drug-using risk. Overall, the behavioral characteristics of this group suggest its members are individuals who are stable but chronic drug users who remain at risk for drug use-related comorbidities and overdose.

Membership in the high intensity drug-using group was associated with younger age and self-reports of injecting drugs greater than once per day. Relative to the low intensity drug users, sharing needles and the use of a variety of drugs, including heroin and cocaine separately, injecting both together as speedball, and smoking crack were associated with group membership. High frequency of poly-drug use and needle sharing is not only associated with longer time to cessation [33] but puts individuals at risk for the medical consequences of chronic substance abuse including HIV transmission or acquisition and poor treatment outcomes [35].

Surprisingly, members of the consistently high drug-using trajectory were less likely to be infected with HIV. Our analysis demonstrated that individuals who are high-risk users are young, intense drug users who remain at risk for HIV acquisition. In ALIVE, the risk of acquiring HIV from injection drug use has

declined in recent years [36]. As a result, there is less circulating HIV and the risk for transmission from a single injection event has reduced. The paradoxical reduced HIV prevalence among high intensity users may represent a cohort effect of younger more intense users with distinct social networks from older users [37] who, by nature of declining HIV prevalence have been spared from acquiring HIV. However, as we have seen with hepatitis C infection, HIV risk may simply be deferred rather than obviated [38]. Our results suggest that these methods could be used in drug treatment trials to calculate daily intensity of use and to capture how intensity relates to other drug using related behaviors (e.g. participation at shooting galleries or sharing needles).

Drug-seeking behavior often conflicts with the health promoting goals of safer sex, safer injecting, and adherence to recommended treatments. Our adjusted analysis demonstrated that the odds of having medical insurance and of attending outpatient appointments were reduced for those classified as high intense drug users relative to low intensity drug users even after adjustment for potential confounders. Our EMA-defined risk groups displayed clinical relevance as evidenced by their ability to predict engagement in care; moving forward, these risk groups could help with targeting of resources for those who have difficulties of remaining engaged in care.

In addition to relatively small sample size, we were limited in this analysis by examination of only time-fixed baseline factors and behavioral variables as predictors of class membership. The latter was done intentionally in order to determine what stable factors predicted drug use, as inclusion of time-varying covariates would have only affected the shape of the trajectory rather than membership in the groups [29]. Additionally, there may be a concern that our study population consists of mostly older individuals who may be maturing out of their drug use and/or beginning to transition to use of prescription drugs rather than injection of street drugs. While this may be true, our study population is representative of the aging population of drug-users in Baltimore, MD and many other cities nationally (e.g., Philadelphia, Newark, Detroit)[39].

To our knowledge, this is one of the first mHealth analyses to use semi-parametric growth mixture models with EMA data to examine sub-populations of heroin and cocaine users. While growth mixture modeling has been previously used to describe trajectories of drug use and cessation, these analyses have been retrospective with decades of follow-up [21, 23] and did not employ ecological momentary assessment methods. Studies have examined latent classes of drug use [22, 40-42] where the goal was to create meaningful subgroups (or latent classes) of drug use based on similarities in responses to a set of indicators but did not describe the pattern of drug use intensity over time (a hallmark of growth mixture modeling). Our analysis described drug use from EMA self-reports and employed

growth mixture models to describe the meaningful groups of drug users that existed in the population.

Although complex, our growth mixture modeling methods still only focus on mean daily drug-using patterns over a relatively short period of observation rather than the specific drug using events. A long term objective of this work is to develop more refined estimates of drug use risk with the goal of reaching smaller time intervals that would better predict immediate behaviors like relapse or missed ART doses.

As previously reported, the EXACT study demonstrates the ability to efficiently and effectively collect high-quality, real-time EMA data in a challenging study population of impoverished urban drug users [25]. As drug use is often not well captured in epidemiological studies, our research demonstrates the ability of mHealth methods to capture drug use in real-time and identify higher-risk drug users. Combined with sophisticated analytic methods, these EMA data described drug use intensity patterns, which have implications for risk behavior and other clinical outcomes including engagement in care. In contrast to the broad range of possibilities of mHealth applications among HIV and substance users, the current EMA analysis should be considered as an initial application. EMA methods improve data collection techniques as well as expand approaches to delivering interventions, such as providing the ability to capture the environmental context of

an individual's drug using experience (Linas et al. under review). In the near future, novel mHealth intervention strategies directed at improving substance abuse and HIV treatment outcomes may incorporate biosensors for drug use or adherence monitoring and geographical positioning systems for location-based individualized ecologic momentary interventions.

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Table 3.1: Baseline characteristics of EXACT participants*

Characteristic	N	%
Median Age, IQR	48.5 (43-53)	-
Male	58	52
African American	98	90
Never Married	66	61
High School Education	44	40
Alcohol use	71	65
CES-D>23	26	23
Cigarette use	91	83
<1/2 pack cigarettes per day	20	18
>1/2 pack cigarettes per day	71	65
Income<\$5,000	83	77
Homeless	9	8
Medical Insurance	93	85
Have a primary care doctor	97	89
Drug abuse, DAST>16	6	18
Methadone Treatment	26	23
Marijuana use	27	24
Speedball use*	26	23
Heroin use (any route) ^Δ	52	46
Cocaine use (any route) ^Δ	54	47
Hepatitis C positive	94	86
HIV positive ⁺⁺	64	59
Median CD4 (IQR) ⁺	360.5(239-529)	-
Viral Load>500 ⁺	35	55

* All baseline characteristics represent behavior within the 6 months prior to the start of EXACT

^Δ Recent drug use was part of the inclusion criteria for Field Trials 3 & 4. Drug use includes any route of administration (smoking, snorting, and injecting).

⁺⁺ HIV+ status was part of the inclusion criteria for Field Trials 3 & 4.

⁺ CD4 & viral load based on HIV-infected participants only.

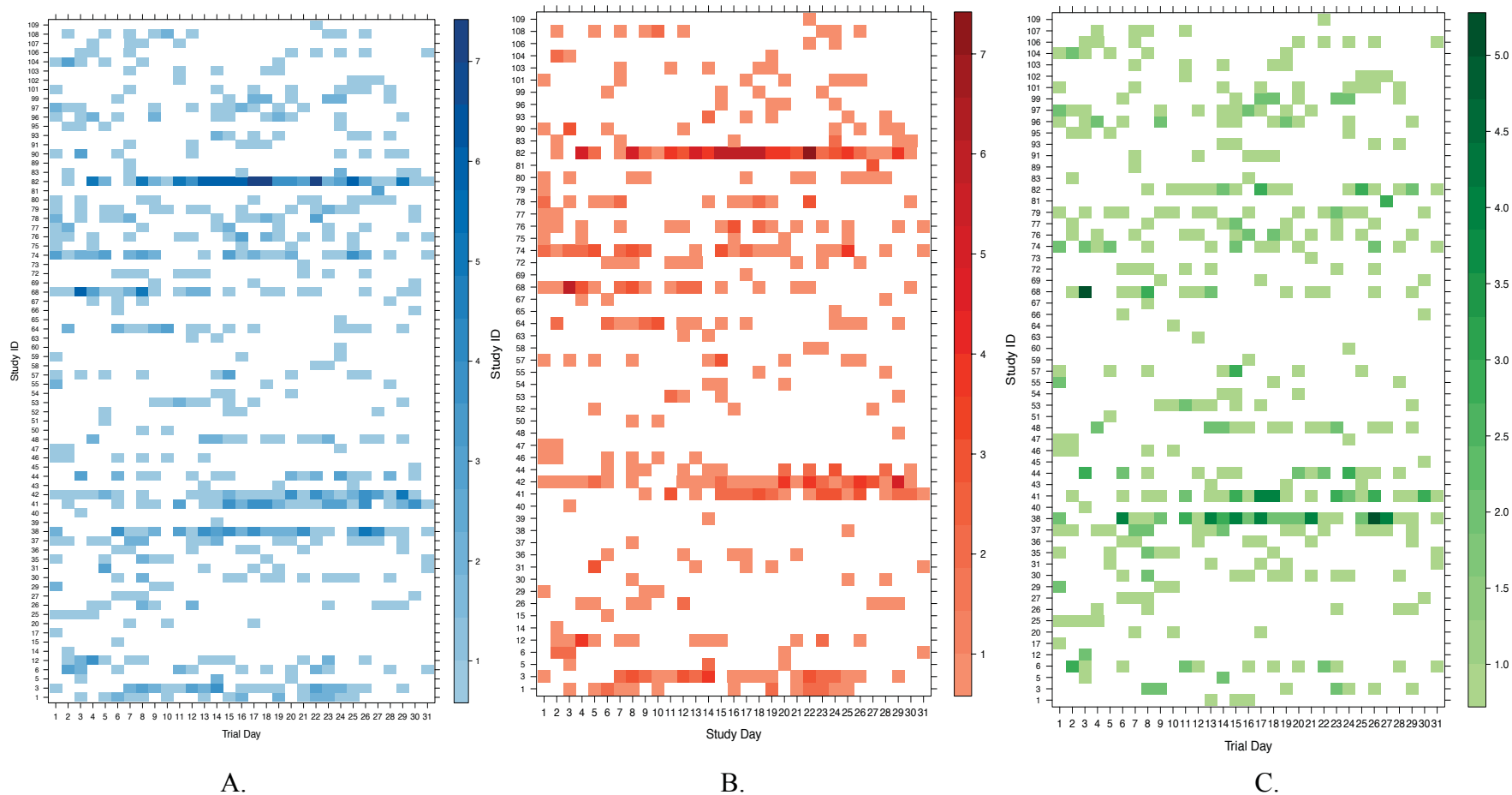


Figure 3.1: Lattice plots of individual drug use intensity by day and drug type

Panel A: Any heroin or cocaine use intensity by trial day. B. Any heroin use intensity by trial day. C. Any cocaine use intensity by trial day. Individuals are represented on the y-axis and the intensity of the color indicates the intensity of self-reported drug use for any given day (darker colors represent more reports of drug use).

Figure 3.2: 3-Class unadjusted growth mixture model of mean daily drug use in EXACT

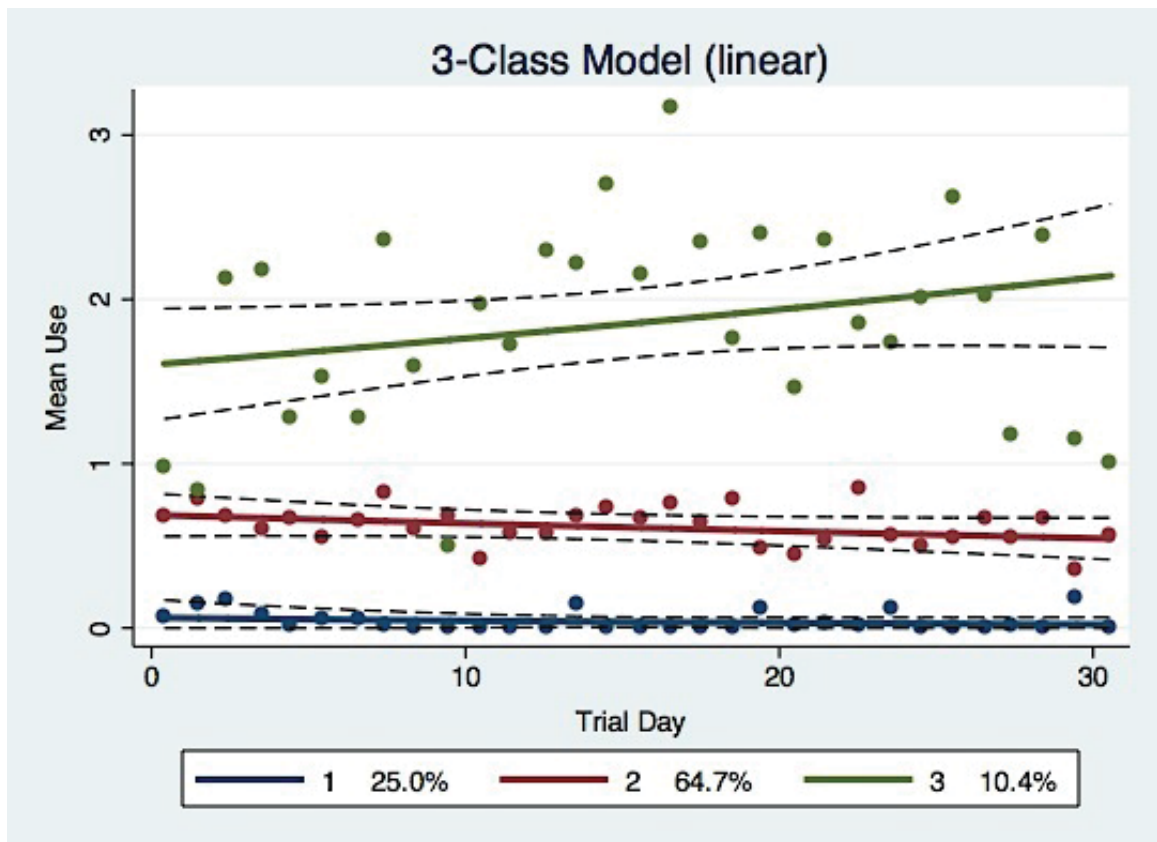


Figure 3.2: Trajectories of mean drug use per day among 109 illicit drug users in the Exposure Assessment in Current Time (EXACT) study. The y-axis represents the mean number of drug use events per day; the x-axis represents each day of the trial. The solid lines represent the predicted mean use per day given group membership with their respective 95% confidence intervals shown as dotted black lines. The solid dots represent the observed mean use per day given group membership. The 3 groups (and proportion of total population within each group) represent: blue, low intensity drug use (25.0%); red, moderate intensity drug use (64.7%); green, high intensity drug use (10.4%). All trajectories were modeled linearly.

Table 3.2: Risk factors associated with drug use risk group membership relative to low intensity drug using group*

	EXACT EMA Drug Use Risk Groups					
Risk factor	Group 2-Moderate intensity drug use			Group 3-High intensity drug use		
	Log Odds	SE	p-value	Log Odds	SE	p-value
Demographics						
Age \geq 50	-0.61	0.58	0.2892	-2.11	1.16	0.0685
Female	-0.17	0.55	0.7554	0.60	1.04	0.5641
Black	-0.23	1.02	0.8253	-1.34	1.21	0.2698
Never married	-1.48	0.71	0.0365	-1.28	0.93	0.1706
High school educated	0.24	0.59	0.684	-1.41	1.16	0.2227
Income \leq \$5,000	0.99	0.64	0.1248	1.33	1.18	0.2619
Homeless	-1.06	0.84	0.2072	-0.72	1.39	0.6039
Any alcohol use	0.29	0.62	0.6438	0.72	0.95	0.4475
Any cigarette use	0.62	0.71	0.3829	17.13	3211.04	0.9957
Clinical Characteristics						
Have a usual source of care	-17.00	2878.31	0.9953	-17.31	2878.31	0.9952
Same doctor 90% of the time	-17.26	2984.56	0.9954	-17.42	2984.56	0.9953
Same doctor for at least 2 years	-0.50	0.63	0.4328	-0.12	0.92	0.8983
CES-D \geq 23 ^a	0.17	0.66	0.7979	1.39	0.88	0.1161
HIV	-0.58	0.60	0.34	-1.94	0.95	0.0418
Highly active antiretroviral therapy (HAART)	-12.55	454.98	0.978	-14.92	454.99	0.9739
Hepatitis C antibody positive	0.07	0.83	0.9308	-1.60	1.02	0.1182
Sexually transmitted infections (excluding chlamydia)	-17.31	2593.91	0.99	-10.84428	229.9665	0.9624
Drug use characteristics						
Frequency of daily injection						
<1/day	1.92	0.74	0.009	-14.38	2798.93	0.9959
\geq 1/day	2.17	1.10	0.0492	3.75	1.36	0.006
Shared needles	2.02	1.08	0.063	2.70	1.24	0.0296
Current injector	1.92	0.66	0.0039	2.75	1.00	0.0063
Marijuana use	0.82	0.65	0.2089	-0.11	1.19	0.9261
Snort cocaine	16.03	2805.64	0.9954	16.84	2805.64	0.9952
Snort heroin	18.07	2727.37	0.9947	17.10	2727.37	0.995
Inject cocaine	1.17	0.91	0.2022	2.34	1.07	0.0284
Inject heroin	2.26	0.84	0.0072	3.31	1.13	0.0035
Crack use	2.60	1.07	0.0153	3.25	1.24	0.0092
Speedball use	2.02	1.21	0.0943	2.70	1.33	0.0435
Attended a detox program	17.14	2808.83	0.9951	16.75	2808.83	0.9952
Methadone treatment	-0.29	0.64	0.6453	-1.57	1.51	0.2994
Any other drug treatment program	-0.83	0.78	0.2889	-16.99	3135.07	0.9957
Attended a drug alcohol treatment program	-0.02	0.58	0.9682	-1.34	0.95	0.1578
DAST \geq 16 ^b	0.49	1.33	0.715	0.82	1.68	0.627

*All characteristics represent self-reported behavior within the 6 months prior to the start of EXACT

a. Center for Epidemiologic Studies- Depression Scale

b. Drug Abuse Screening Test

Table 3.3: Unadjusted association of drug use risk and engagement in care at subsequent ALIVE visit

At subsequent ALIVE Visit, did Participant report....	Medical Insurance Status			Attended Outpatient Appointments		
	OR	95% CI	P-value	OR	95% CI	P-value
<i>EMA drug use risk groups</i>						
Low intensity drug use	Ref	Ref		Ref	Ref	
Moderate intensity drug use	0.64	0.13-3.19	0.558	0.64	0.19-2.16	0.476
High intensity drug use	0.13	0.02-0.94	0.043	0.19	0.03-1.04	0.055

*Bold values indicate p-value<0.05

Table 3.4: Adjusted associations of drug use risk and engagement in care at subsequent ALIVE visit^a

At subsequent ALIVE Visit, did Participant report....	Medical Insurance Status			Attended Outpatient Appointments		
	aOR	95% CI	P-value	aOR	95% CI	P-value
<i>EMA drug use risk groups</i>						
Low intensity drug use	Ref	Ref	Ref	Ref	Ref	Ref
Moderate intensity drug use	0.50	0.09-2.89	0.486	0.52	0.14-1.89	0.322
High intensity drug use	0.10	0.01-0.88	0.040	0.13	0.02-0.85	0.033
Female	0.69	0.21-2.33	0.554	2.93	1.07-8.04	0.037
Age \geq 50	1.24	0.32-4.84	0.757	0.68	0.25-1.88	0.460
Homeless	0.62	0.07-5.28	0.663	0.42	0.07-2.58	0.350
Methadone Treatment				0.74	0.23-2.35	0.604
Same doctor for at least 2 years	5.57	1.63-19.05	0.006			

^aModels adjusted for variables with listed values

*Bold values indicate p-value<0.05

Chapter 4:

Capturing illicit drug use where and when it happens: an ecological momentary assessment of the social, physical and activity environment of using versus craving illicit

Abstract

Aims: Understanding the environmental influences of using versus craving (but resisting) illicit drugs can inform interventions to prevent relapse and support cessation.

Design: The Exposure Assessment in Current Time (EXACT) study utilized ecological momentary assessment methods to assess drug use in real-time in participants' natural environments. 109 participants were provided mobile devices and asked to self-report every time they either craved (without using) or used heroin or cocaine for 30-days from November 2008 through May 2013.

Setting: Baltimore, MD

Measurements: For each event, participants answered questions concerning their drug use, current mood, and their social, physical and activity environments. Odds ratios of drug use versus craving were obtained from logistic regression models with generalized estimating equations of all reported events.

Findings: Participants were a median of 48.5 years old, 90% African American, 52% male and 59% HIV-infected. Participants were significantly more likely to report use rather than craving drugs if they were with someone who was using drugs (aOR 1.45, 95% CI: 1.13, 1.86), in an abandoned space (aOR 6.65, 95% CI:

1.78,24.84) or walking/wandering (aOR 1.68, 95% CI: 1.11,2.54). Craving drugs was associated with being with a child (aOR 0.26; 95% CI: 0.12,0.59), eating (aOR 0.54, 95% CI: 0.34,0.85) or being at the doctor's office (aOR 0.31, 95% CI: 0.12, 0.80).

Conclusions: Drug-related activities provided the strongest cues for drug use, while craving was associated with more stable environments. Interactive mHealth methods are capable of describing the drug-using environment and can provide the framework for developing context-sensitive interventions to support cessation and prevent relapse.

Key words: substance use, mHealth, and ecological momentary assessment

Introduction

Substance abuse is a chronic disease often characterized by multiple attempts at abstinence with frequent relapse. It is associated with a range of morbidities as well as deleterious effects on family members and larger society [1-4].

Capturing drug use in epidemiologic studies involves substantial recall bias [5, 6] and often does not quantify the amount or duration of use. Drug use is often self-reported (occasionally verified through biological measures) and typically captures any drug use over long periods of recall (e.g., 6 to 12 months) [7-9]. This broad time frame often misses varying periods of intense or intermittent use and further fails to capture the proximate context of an individual's drug using experience.

Drug-using behavior occurs within a specific organizational and structural environment with outcomes fundamentally linked to both individual and situational and factors [10]. Substance abuse is commonly associated with a chaotic or disordered life, mental illness, financial and legal difficulties, and inadequate housing or transportation [11-13]. Daily environmental cues of drug use remain largely unexamined as risk factors for drug use and barriers to care.

Drug craving has been theorized to have a critical role in drug dependence and relapse, although there have been substantial inconsistencies in data supporting this view [14, 15]. There is clear recognition of the need for more detailed and novel methods for measuring craving (e.g., a virtual reality approach to examine cue

elicited tobacco cravings [16]).

Ecological momentary assessment (EMA) methods collect participant-level data in real time and facilitate responsive communication between providers and patients. EMA is a mobile health (mHealth) method that employs mobile devices (e.g., smartphones or other hand-held devices) to improve health outcomes, healthcare services and public health research. These EMA methods have been utilized in smoking cessation studies [17-23] and among methadone-maintained outpatient drug users [24-28]. EMA provides an ideal method for assessing drug craving by capturing transient ‘states’ rather than summing craving events over time to assess ‘traits’. By collecting real-time data, a more vibrant and comprehensible understanding of the drug-using environment can be generated. Knowing the proximate determinants of drug use and how they differ from drug craving and relapse can inform why some persons are able to maintain cessation while others are not. The current study utilizes EMA methods to ascertain the social, physical, activity and psychosocial environment associated with drug use compared to drug craving in a community sample of drug users in Baltimore, MD.

Methods

EXACT study participants

Exposure Assessment in Current Time (EXACT) study participants were recruited from the AIDS Linked to the IntraVenous Experience (ALIVE) study, an on-

going, community-recruited, observational cohort of persons with a history of injecting drugs in Baltimore, MD [29]. The ALIVE cohort is community- rather than clinic-based, thereby avoiding selection bias toward persons seeking or accessing care. Details of the EXACT study have been previously described [30], and included four successive trials conducted from November 2008 through May 2013. Each trial was planned to follow 30 participants each for 30 days.

Eligibility criteria for the EXACT study included current enrollment in ALIVE and the ability to understand and follow directions on a personal digital assistant (PDA) or mobile phone. Individuals were excluded if they had any medical conditions that would prevent them from operating the hand held device (e.g., vision or hearing impairment) or failed to attend the screening appointment where they were trained on device use.

In each trial, the specific inclusion criteria regarding drug use and HIV status were varied slightly to ensure a diverse sample; both injection and non-injection drug users were included. In Trial 1, selection was made to balance the numbers of participants that reported heroin or cocaine use within the past month (defined as recent drug use) with those that were not currently using drugs. In Trial 2, all participants reported heroin or cocaine use within the prior three months. While HIV status was not a recruitment criterion in the first two trials, Trial 3 included only HIV-infected participants with recent heroin and cocaine use. These same

criteria were also used in Trial 4, but the data collection was transitioned from a PDA to a smartphone platform [30].

The Johns Hopkins School of Public Health Institutional Review Board approved the study protocol. All participants provided written informed consent.

Participants were informed that involvement (or non-involvement) in EXACT would in no way affect their participation in ALIVE.

Data Collection

Hand-held devices delivered four prompts to complete surveys at random times daily between 8am and 9pm (known as random-prompt entries), and one end-of-day (around 9 pm) survey for 30 days of observation. Participants were also asked to self-initiate a survey and self-report each time they either craved (but refrained from using) or used heroin or cocaine (or both) in any manner (smoked, snorted or injected); these responses represent event-contingent entries. Heroin only and cocaine only reports incorporated all reports of heroin or cocaine use (including those jointly with another drug).

For each event, participants answered questions concerning their drug use, current mood, social, physical and activity environment, using survey instruments adapted from previous EMA studies [24-28]. Participants had 30 minutes to complete an

event-contingent survey to ensure responses were recorded in real-time. All data used in the present analyses are from event-contingent entries.

For Trials 1-3, participants were provided personal digital assistants (PDA, Palm Z22, Palm, Inc., Sunnyvale, CA, USA) running applications developed using Satellite Forms software (<http://www.satelliteforms.net/>). All PDA programs were disabled except for study-required applications. In Trial 4, participants were provided an Android Smartphone (Motorola Droid X2), running an application developed using the Electronic Mobile Open-source Comprehensive Health Application (*eMOCHA*) platform, created at Johns Hopkins School of Medicine. Previously, *eMOCHA* was used to support community health workers in resource-limited settings heavily impacted by HIV [31].

Baseline characteristics were obtained from audio-computer assisted self-interviews (ACASI) completed at enrollment into EXACT and/or from the prior ALIVE study visit. In addition to sociodemographic variables (e.g., age, sex, race, education, marital status, employment, income, homelessness and health insurance status), baseline data collection included self-reported alcohol, tobacco and illicit drug use [Drug Abuse Screening Test (DAST)] and depressive symptoms [Center for Epidemiologic Studies- Depression Scale (CES-D)] in the prior six-months [32].

To reduce participant burden, event-contingent time-varying questions required only a “yes /no” response. These EMA variables included:

Social environment: Whom participant was with during an event: friend, acquaintance, family member, a stranger, a spouse, and a child, alone, someone currently using drugs or an “out-the-door partner” (someone a drug user visits for the purpose of using or buying drugs).

Activity environment: What activity was participant engaged in when they reported an event: socializing, sleeping, eating, shopping, planning/thinking, engaging in recreational activities, drinking alcohol, using tobacco, offered drugs, saw or were with someone using drugs, saw drug paraphernalia, handling \$10 in cash, engaging in illegal activity, or “copping” (exchanging small goods or services for obtaining drugs).

Physical environment: Participant’s physical location when reporting an event: home, another’s home, car, bus or train, outdoors, church, job/working, restaurant, abandoned space, doctor’s office, store, shelter, bar, or “cop” spot (where someone goes to buy drugs).

Psychosocial environment: Participant’s mood or motivation when reporting an event. Responses to the question, “How do you feel right now?” included “happy”, “stressed”, “tired”, “relaxed”, “bored”, “irritated”

and “none of the above”. Responses were not mutually exclusive, allowing participants to mark all that applied. Motivational variables included responses to whether participants “wanted to see what would happen if you took just one hit” or “wanted to use out of the blue”.

Analysis

This analysis examined the event-contingent entries using logistic regression models with generalized estimating equations (GEE) and autoregressive covariance structures to model the outcome of drug use vs. drug craving events (SAS Proc Genmod). GEE adjusted for the correlation of repeated measures within each subject over the 30-day period of follow-up. Variables selected for the final models of drug use vs. drug craving were chosen through step-wise regression. First, separate univariate models were run for each of the variables in the baseline characteristics, social, physical and activity environment and psychosocial variable categories.

Variables with p -values < 0.1 in univariate analyses were included in separate adjusted models for each of the different variable groups. Fully adjusted models for drug use and those stratified by heroin (i.e., heroin use vs. heroin craving) and cocaine use (i.e., cocaine use vs. cocaine craving) were generated to include all variables with p -values < 0.1 from any of the adjusted group models. Final models for drug use, including heroin and cocaine use, were built to achieve parsimony and included statistically significant (p -value < 0.05) variables from the fully

adjusted models. All models included a control term for the number of records that each participant contributed to the dataset. An HIV stratified analysis was repeated using the same methods. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

Table 4.1 describes baseline characteristics for the 109 EXACT participants. The median age was 48.5 years (interquartile range (IQR) 43-53 years), 90% were African American, 52% male and 59% were HIV infected. At baseline, 23% of participants reported recent methadone treatment and 83% reported smoking cigarettes daily in the six-months prior to baseline assessment. A total of 2,798 events were reported; 1,954 (69.8%) were drug craving and 844 (30.2%) were drug use events. Of the drug use events, 351 events were exclusively heroin (41.6%), 289 events were exclusively cocaine (34.2%) and 201 events were reports of using both heroin and cocaine (23.8%). Over the 30 days, the median number of self-reported craving events was 8 (IQR 5-14) and the median number of self-reported drug using events was 4 (IQR 1-10).

Table 4.2 presents multivariable models A-E for the three outcomes of: drug use (n=844) vs. crave (n=1,954), heroin use (n=552) vs. heroin crave (n=1,284) and cocaine use (n=490) vs. cocaine crave (n=926). Each model describes odds ratios adjusted (aOR) for baseline characteristics, social, physical, activity and

psychosocial environment variables. Variables included in these multivariable models were those that were significant in univariate analyses with $p\text{-value} \leq 0.1$.

Among baseline factors (Table 4.2, Model A), participants with recent methadone treatment reported 27% of events as drug using and 73% as drug-craving events. In multivariable analyses, older age and recent methadone use were significantly associated with decreased odds of drug use (Table 2, Model A). Baseline reports of substance use included cigarette, heroin and cocaine use and all increased the odds of drug use over craving by 2-3-fold.

Social environment factors (Table 4.2, Model B), including children being present, reduced the odds of using drugs while being around someone else using drugs increased the risk for using. Children were present at 11.5% of drug use events and 88.5% of craving events. Specifically, cocaine use increased significantly if participants reported being with an out-the-door- partner, if their spouse was present at the time of the event, or if someone had offered them drugs.

With respect to the activity environment (Table 4.2, Model C), reports of eating around the time of the event were associated with reduced drug use. The likelihood of drug use increased with reports of using tobacco, handling \$10 in cash and seeing drug paraphernalia. Tobacco use was reported at 92% of drug

using events. Events where seeing drug paraphernalia was reported, 48% were drug-using events and 52% were drug-craving events.

Physical environments (Table 4.2, Model D) that were associated with a reduced likelihood of using drugs included reports of being in a car, bus or train, at the doctor's office, or at work. Reports of being at home, walking or wandering and being in an abandoned space at the time of the reported event were associated with increased odds of drug use. More drug use than drug craving events occurred in abandoned spaces (81% were drug use events, 19% were drug craving events).

Regarding participants' psychosocial environment around the time of the event (Table 4.2, Model E), reports of anger were associated with reduced drug use, while persons reporting being in pain because they needed a hit were 5-times as likely to use rather than crave drugs, especially with heroin use.

Figures 4.1-4.3 depict the final multivariable models combining significant variables from these prior models for: any drug use (Figure 4.1), heroin only (Figure 4.2) and cocaine only (Figure 4.3). For any drug (Figure 4.1), drug use was significantly reduced with reports of being with a child (aOR 0.26, 95% CI: 0.12,0.59), at the doctor's office (aOR 0.31, 95% CI: 0.12,0.80) or eating (aOR 0.54, 95% CI:0. 34,0.85) at the time of the event. Recent methadone treatment was marginally associated with reduced drug use (aOR 0.57, 95%CI:0. 30,1.07).

Factors associated with an increased likelihood of drug use included a 2-fold increase with recent heroin use (aOR 2.49, 95% CI: 1.34,4.61), a 3-fold increase with seeing drug paraphernalia (aOR 3.07, 96% CI: 1.97,4.80) and a 6-fold increase with being in an abandoned space at the time of the event (aOR 6.65, 95% CI: 1.78, 24.84). Additional predictors of any drug use in the final adjusted model included: using tobacco at the time of the reported event (aOR 2.27, 95%CI: 1.37,3.78), handling \$10 in cash (aOR 1.70, 95% CI: 1.11,2.59), being with someone who was using drugs (aOR 1.45, 95% CI: 1.13,1.86), being with your spouse (aOR 2.09, 95% CI: 1.22,3.59), being a home (aOR 1.68, 95% CI: 1.00,2.82) and walking/wandering (aOR 1.68, 95% CI: 1.11,2.54) at the time of the event.

While there was some overlap between the overall final models for any drug use, heroin only and cocaine only (e.g., protective associations with being around children or doctors office, increased risk with seeing drug paraphernalia; Figures 4.1- 4.3), there were several factors uniquely associated with the type of drug used. For heroin use events, as might be expected, reports of heroin use in the period just before study entry increased use risk, while recent methadone treatment reduced risk. There were specific demographic differences as well. African Americans were less likely than Caucasians to use heroin (aOR 0.47, 95% CI: 0.19,0.15), while older adults (≥ 50 years of age) were less likely to use cocaine (aOR 0.39, 95% CI: 0.22,0.68). In addition to increased risk associated with

activities like walking and wandering and seeing others use drugs, tobacco use was strongly associated with heroin use, including both recent intensity of smoking prior to study entry and cigarette smoking concurrent with the event. In contrast, social context appeared uniquely associated with increased likelihood of cocaine use, including being in the presence of others using drugs, a spouse, or an “out-the-door” partner (aOR 7.90, 95% CI: 1.45,43.01). After accounting for other sociodemographic and environmental factors, psychosocial factors were not significantly associated with drug use overall or with using heroin or cocaine only.

A restricted analysis of HIV infected individuals revealed that being with a child and recent methadone treatment were predictors of drug craving whereas using tobacco, handling \$10 cash, seeing someone use and past heroin use were predictors of drug use. The point estimates (not shown) were similar to those in the final drug use vs. craving model in Figure 4.1. Additional sensitivity analyses restricting heroin and cocaine use to exclusively heroin or cocaine (excluding reports of mixed heroin/cocaine use events) resulted in similar estimates as the heroin and cocaine analyses in Figures 4.2 and 4.3.

Discussion

This ecological momentary assessment study provides real-time data to characterize the social, physical and activity environment of drug users where and

when it actually occurs. Among 109 participants followed for a 30-day period, we demonstrated distinct drug using and drug craving environments. Our data suggest that drug use is facilitated over craving in less structured social and physical environments. Further, the presence of drug-related activity appears often to serve as a catalyst for illicit drug use. Our study provides novel data that individual, social, and physical environmental factors during craving events may mitigate against drug use. These findings implicate the need to strongly consider proximate environmental factors in designing individualized interventions to reduce relapse to drug use.

Less structured social and physical environments including reports of walking and wandering or being in an abandoned space at the time of an event were highly associated with drug use rather than drug craving. Physical environments where drug use may readily occur have been theorized to represent environments impacted by disadvantage and deprivation, lack structure and present drug exposure opportunities [33-35]. Practically, informal physical environments may give rise to drug use because individuals can wander without difficulty where drug sales are common, readily locate and access abandoned spaces and more easily evade law enforcement [36-38]. Abandoned buildings may help protect from police intrusion but importantly, will lack facilities to ensure clean injection equipment[39].

Drug-related activities provided the strongest cues for drug use in this analysis. Activities including handling small amounts of cash, seeing drug paraphernalia or being around others using drugs were strongly associated with participants reporting drug use. These associations suggest use is intensely influenced by situational drug triggers, which may be difficult to avoid in some heavily impacted communities. These real-time EMA data are consistent with our prior reports from the ALIVE cohort that moving from a highly deprived neighborhood to a less deprived one is among the strongest predictors of maintaining long-term cessation [33]. Exposure to drug use, through individuals or paraphernalia not only indicates drug availability but also provides the opportunity to maintain their using habits. Reports of handling \$10 in cash reflect the nature of our participants' cash-based financial lives, however, the strong association with using drugs suggests it may also be a trigger for drug use. It has been previously reported that the likelihood of handling cash increases in the hours preceding cocaine use and although this may reflect transactions needed to buy cocaine, it could also indicate that handling cash triggers the temptation to use drugs [26].

We also found that being at home or with a spouse was an environment where drug use easily facilitated. Although different from an abandoned space- a home is controlled by an owner or renter and is only accessible to acquaintances of the home. Using drugs at home with or without a spouse may represent a shared drug addiction where drug use is enabled [40]. These associations are likely to be

bidirectional with individuals seeking certain settings when they plan to use and certain environmental factors facilitating use.

Recent methadone treatment was associated with drug craving. An expected finding, methadone is effective treatment of opioid addiction and is a proven strategy to support heroin abstinence and to reduce injection-related risk behavior and other undesired social behaviors, such as criminal activity [41]. Conversely, self-reports of heroin use and cigarette smoking within the six months prior to the start of EXACT were predictors of using drugs and heroin. The prevalence of cigarette smoking among illicit drug users is among the highest reported from any population [42] and illicit drug users may experience stronger physiological dependence to nicotine as a result of their addiction [42-44]. Understanding the dynamics of tobacco and illicit drug use warrants further investigation, however, our analysis suggests a considerable need for combination therapy targeting both illicit drug use and smoking [45-47]. Timely integration of smoking cessation into drug treatment programs could potentially help support abstinence from illicit drug use while addressing the disproportionate burden of tobacco use in this population.

Our analysis showed that drug craving without using occurred more frequently in structured physical and social environments. These situations included being with a child, at the doctor's office, at work, eating or in formal transport such as a car, bus or train. Structured activities like having a job, eating regular meals, spending

time with a child, and attending clinic appointments are likely indicators of a more stable lifestyle and suggest a more controlled environment with responsibilities for self-care and care for others.

It has been suggested that craving and relapse may represent independent phenomena and that reports of craving may not predict relapse [48, 49]. However, it is possible that craving represents episodes where individuals have motivation to use but other environmental factors impeded use. Building on this premise, our findings suggest that EMA may be utilized to tailor drug treatment interventions. By identifying social, physical and activity environments associated with craving and drug use, drug users could be counseled and supported to avoid such settings and to facilitate time in environments that reduce the probability of drug use.

Although we demonstrate a clear distinction between the drug-using and drug-craving environments, this analysis is limited to event monitoring and therefore can only generate information concerning drug use or craving events. With this event-focused analysis, it is not possible for example, to distinguish between subjects who spend regular amounts of time with other drug users from subjects who are only around drug users when they choose to use.

As previously reported, the EXACT study demonstrated the ability to efficiently and effectively collect high-quality, real-time EMA data in a challenging study

population of drug users [30]. In this study, we provide evidence that EMA methods represent a novel interactive mHealth strategy for capturing the drug using experience in natural settings. The next step for these methods is to move beyond real-time data collection towards tailored interventions in response to these environmental cues. As our understanding of the drug-using environment improves, ecological momentary interventions (EMI), such as those that utilize GPS to alert and divert drug users when they approach a location that was previously a spot for drug use, or the delivery of motivational or cognitive behavioral therapies in real-time as personalized, context-sensitive interventions, hold great promise to improve drug treatment and prevent drug relapse.

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Table 4.1: Baseline characteristics of EXACT participants*

Characteristic	N	%
Median Age, IQR	48.5 (43-53)	-
Male	58	52
African American	98	90
Never Married	66	61
High School Education	44	40
Alcohol use	71	65
CES-D>23	26	23
Cigarette use	91	83
<1/2 pack cigarettes per day	20	18
>1/2 pack cigarettes per day	71	65
Income<\$5,000	83	77
Homeless	9	8
Medical Insurance	93	85
Have a primary care doctor	97	89
Drug abuse, DAST>16	6	18
Methadone Treatment	26	23
Marijuana use	27	24
Speedball use*	26	23
Heroin use (any route) ^Δ	52	46
Cocaine use (any route) ^Δ	54	47
Hepatitis C positive	94	86
HIV positive ⁺⁺	64	59
Median CD4(IQR) ⁺	360.5(239-529)	-
Viral Load>500 ⁺	35	55

* All baseline characteristics represent behavior within the 6 months prior to the start of EXACT

^Δ Recent drug use was part of the inclusion criteria for Field Trials 3 & 4. Drug use includes any route of administration (smoking, snorting, and injecting).

⁺⁺ HIV+ status was part of the inclusion criteria for Field Trials 3 & 4.

⁺ CD4 & viral load based on HIV-infected participants only.

Table 4.2: Multivariable adjusted odds ratios of drug, heroin and cocaine use vs. crave

	Drug Use vs. Drug crave				Heroin use vs. Heroin crave				Cocaine use vs. Cocaine crave			
MODEL A: BASELINE CHARACTERISTICS[□]	aOR	95% CI		P-value	aOR	95 % CI		P-value	aOR	95 % CI		P-value
Female					1.51	0.84	2.72	0.173				
Age≥50	0.55	0.29	1.04	0.0652					0.42	0.22	0.81	0.0089
Black	0.85	0.34	2.12	0.7279	0.55	0.28	1.08	0.0808				
HS Education	0.68	0.41	1.14	0.1435	0.97	0.6	1.56	0.8876	0.84	0.48	1.47	0.5457
Ever Married					0.74	0.43	1.29	0.2921	0.72	0.37	1.39	0.3236
# Packs/day of Cigarettes												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref				
<1/2 pack/day	2.06	0.66	6.4	0.2112	3.77	1.46	9.73	0.0061				
>1/2 pack/day	1.2	0.35	4.15	0.7686	1.11	0.38	3.22	0.8476				
CESD≥23					0.95	0.38	2.37	0.9128				
Methadone treatment	0.3	0.18	0.51	<0.0001	0.33	0.15	0.71	0.0043				
Any heroin	3.4	1.59	7.3	0.0017	3.48	1.44	8.4	0.0055	2.51	1.07	5.88	0.0337
Any cocaine	2.21	1.28	3.81	0.0043	1.59	0.81	3.11	0.1745	2.67	1.37	5.21	0.004
Any Speedball	0.77	0.4	1.47	0.4268					0.88	0.4	1.94	0.7459
	Drug Use vs. Drug crave				Heroin use vs. Heroin crave				Cocaine use vs. Cocaine crave			
MODEL B: SOCIAL ENVIRONMENT	aOR	95% CI		P-value	aOR	95 % CI		P-value	aOR	95 % CI		P-value
With an Acquaintance												
Alone												
With family									0.63	0.33	1.21	0.165
With a child	0.25	0.14	0.43	<0.0001	0.17	0.08	0.4	<0.0001	0.31	0.16	0.59	0.0004
With a friend	1.06	0.76	1.48	0.7322	1.09	0.77	1.56	0.6157				
With an out-the-door partner	2.28	0.81	6.42	0.1174					6.69	1.38	32.4	0.0182
With your spouse	1.78	1.09	2.92	0.0218					2.11	1.26	3.53	0.0044
With a stranger												
Were offered drugs	1.74	0.98	3.1	0.0607	1.43	0.76	2.67	0.263	2.09	1.13	3.86	0.0182
With someone who is using	2.52	1.78	3.57	<0.0001	2.51	1.53	4.13	0.0003	2.65	1.8	3.92	<0.0001

- All baseline characteristics represent behavior within the 6 months prior to the start of EXACT
- Bold values indicate p-value<0.1
- All models are adjusted for variables with listed values
- Empty cells represent variables not included in multivariable models as they were not statistically significant (p<0.1) in univariate analyses

Table 4.2: Continued

	Drug Use vs. Drug crave				Heroin use vs. Heroin crave				Cocaine use vs. Cocaine crave			
MODEL C: ACTIVITY ENVIRONMENT	aOR	95% CI		P-value	aOR	95 % CI		P-value	aOR	95 % CI		P-value
Eating	0.6	0.43	0.84	0.0027					0.55	0.36	0.84	0.0059
Planning	0.99	0.61	1.61	0.9819	1.04	0.61	1.76	0.8852	0.96	0.59	1.54	0.8509
Handled \$10 in cash	1.54	1.06	2.24	0.0242	1.56	0.98	2.5	0.0625	1.47	0.89	2.43	0.1317
Copping	1.72	0.99	3.00	0.0548	1.29	0.62	2.69	0.4905	1.73	0.71	4.21	0.2279
Saw someone use	1.17	0.74	1.83	0.5087	1.55	1.04	2.31	0.0312	2.33	1.33	4.07	0.003
Saw drug paraphernalia	3.56	1.91	6.63	<0.0001	4.2	2.21	7.97	<0.0001	2.27	1.24	4.12	0.0074
Socializing	0.97	0.66	1.42	0.8828	0.87	0.63	1.22	0.4273	0.97	0.6	1.58	0.9076
Using tobacco	2.44	1.51	3.96	0.0003	3.19	1.51	6.76	0.0024	1.84	1.07	3.16	0.028
Sleeping	0.96	0.65	1.41	0.8254					0.77	0.44	1.37	0.3745
Doing illegal activities	0.81	0.29	2.23	0.681					1.08	0.39	3.04	0.8796
	Drug Use vs. Drug crave				Heroin use vs. Heroin crave				Cocaine use vs. Cocaine crave			
MODEL D: PHYSICAL ENVIRONMENT	aOR	95% CI		P-value	aOR	95 % CI		P-value	aOR	95 % CI		P-value
At your home	1.83	1.13	2.97	0.0137					1.81	1.11	2.95	0.017
In a car/bus/train	0.32	0.15	0.68	0.0029	0.34	0.18	0.64	0.0008	0.25	0.1	0.6	0.0018
At the doctor's office	0.19	0.06	0.62	0.0061	0.16	0.04	0.61	0.0078	0.16	0.05	0.51	0.002
At a restaurant	3.78	1.04	13.82	0.044	8.5	3.26	22.2	<0.0001	2.07	0.42	10.34	0.3739
At your work place	0.34	0.18	0.66	0.0012	0.53	0.23	1.24	0.1452	0.55	0.21	1.44	0.2211
At a store	0.38	0.18	0.79	0.0092	0.33	0.14	0.75	0.0084				
Wandering/walking	2.78	1.84	4.21	<0.0001	3.31	2.17	5.05	<0.0001	2.04	1.34	3.11	0.0009
In an abandoned space	7.94	3.64	17.31	<0.0001	4.44	1.77	11.19	0.0015	7.52	3.44	16.42	<0.0001
	Drug Use vs. Drug crave				Heroin use vs. Heroin crave				Cocaine use vs. Cocaine crave			
MODEL E: PSYCHOSOCIAL ENVIRONMENT	aOR	95% CI		P-value	aOR	95 % CI		P-value	aOR	95 % CI		P-value
You were angry	0.41	0.2	0.87	0.0196	0.47	0.18	1.2	0.115				
You were in pain because you needed a hit	5.17	2.21	12.05	<0.0001	8.94	4.07	19.62	<0.0001	2.80	1.05	7.45	0.0388
Wanted to see what would happen if you took one hit	0.81	0.45	1.46	0.4767								
Wanted to use out of the blue	1.42	0.65	3.11	0.375	0.79	0.34	1.85	0.5839	3.12	0.82	11.83	0.0944

- All models are adjusted for variables with listed values and bold values indicate p-value<0.1
Empty cells represent variables not included in multivariable models, as they were not statistically significant (p<0.1) in univariate analyses

Figure 4.1: Odds ratio of drug use vs. drug craving^a

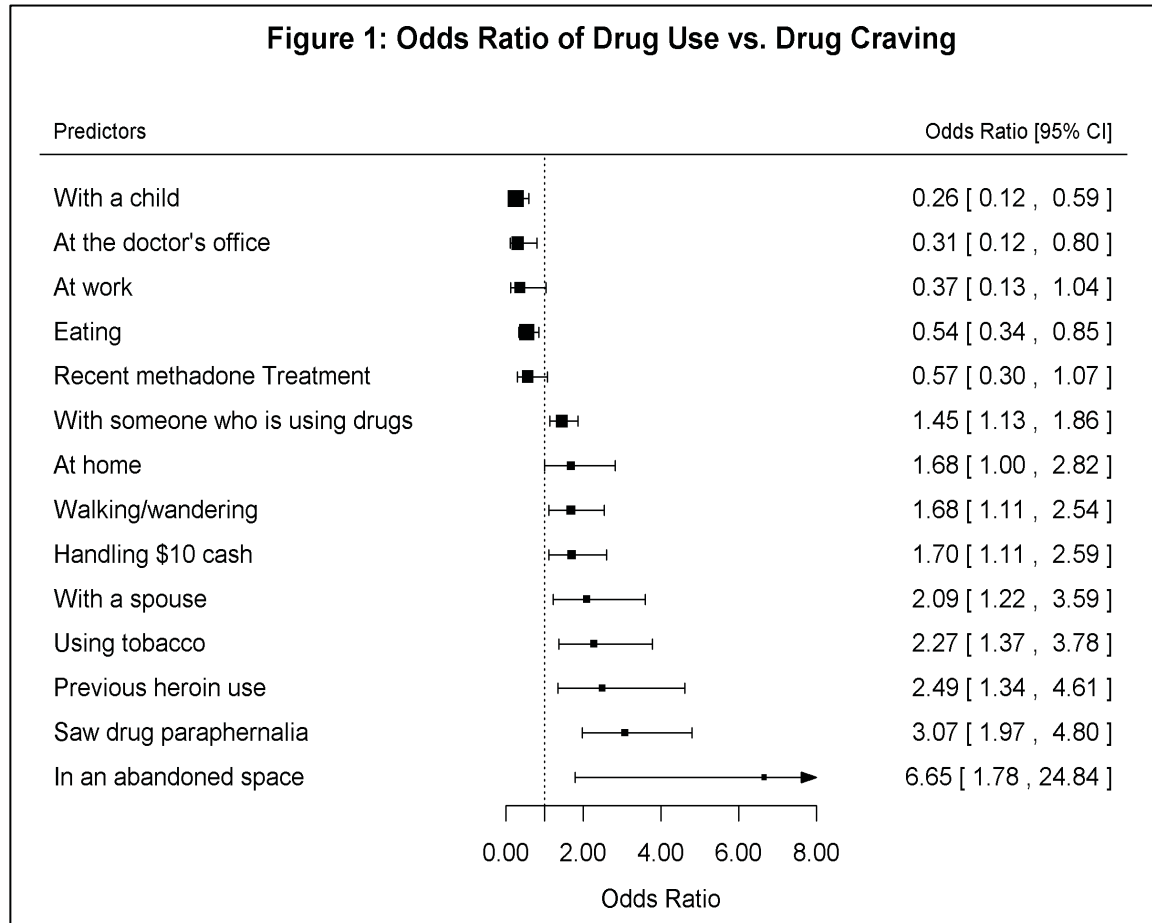


Figure 4.1: Drug use refers to any drug use reported in real-time and is defined as the use of heroin or cocaine, in any manner, over the 30-day EXACT study period.

^aModel adjusted for all variables listed

Figure 4.2: Odds ratio of heroin use vs. heroin craving^a

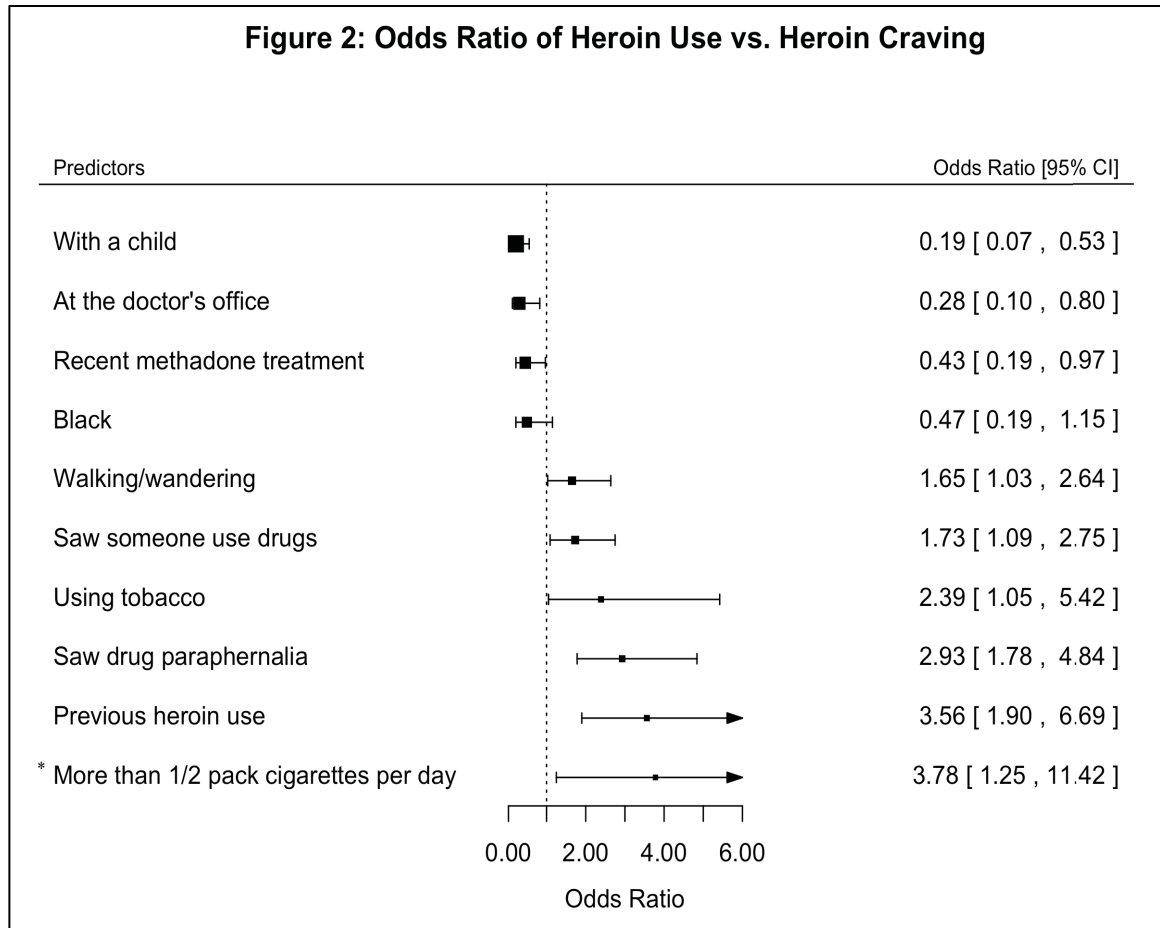


Figure 4.2: Heroin use refers to all uses of heroin reported in real-time including those jointly with another drug, in any manner, over the 30-day EXACT study period.

* Cigarette packs/day was assessed at baseline represents use within the 6-months prior to the start of EXACT

^a Model adjusted for all variables listed

Figure 4.3: Odds ratio of cocaine use vs. cocaine craving^a

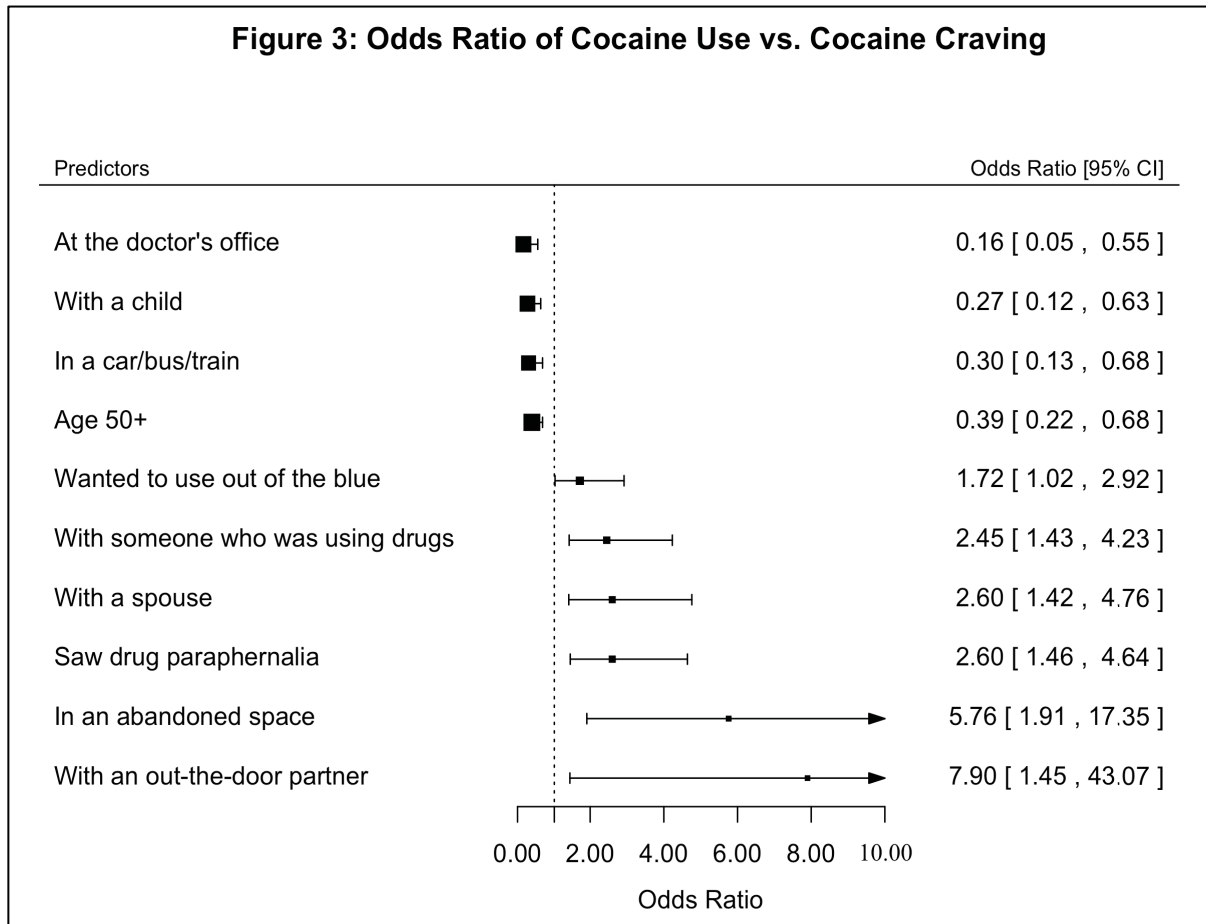


Figure 4.3: Cocaine use refers to all uses of cocaine reported in real-time including those jointly with another drug, in any manner, over the 30-day EXACT study period.

^aModel adjusted for all variables listed

Chapter 5:

Conclusions and Future Directions

Summary of Results

Illicit drug users are a known challenging population to research. Identifying, recruiting and retaining drug users is problematic in epidemiologic, behavioral and clinical research studies. Additionally, individuals with substance abuse problems tend to have a range of vulnerabilities that place them at increased risk for relapse as well as becoming HIV infected and failing to achieve desired treatment outcomes of viral suppression [1, 2]. The motivation behind this dissertation stemmed from the need for novel methods to understand illicit drug users and the context of the drug-using environment to improve health outcomes among this high-risk population.

The Exposure Assessment in Current Time study was the first ecological momentary assessment (EMA) study to examine the drug-using environment among community-dwelling, out-of-treatment drug users, utilizing hand-held mobile devices. This dissertation examined how mHealth methods can capture and quantify self-reported drug use, described the heterogeneous patterns of drug use and their associations with engagement in care, as well as demonstrated the role of contextual factors in determining drug using risk behavior.

Chapter 2 examined the concordance and inter-rater reliability of ecological momentary assessment methods compared to well understood and validated methods of audio computer-assisted self-interview (ACASI) and biological sweat patches for assessing drug use [3-6]. Table 5.1 summarizes the different features of each method and how they each capture drug use. Our analyses demonstrated that EMA methods have strong concordance for both biological sweat patch and ACASI-based methods for capturing heroin and cocaine use. The overall percent agreement between EMA and sweat patch methods for cocaine use was 70%, while the overall percent agreement between EMA and ACASI methods for cocaine use was 77%. The percent agreement between EMA and sweat patch methods for heroin was 72%, while the overall percent agreement between EMA and ACASI methods for heroin use was 79%.

The kappa statistic is a measure of inter-rater reliability that takes into account the agreement occurring by chance. The kappa statistics were slightly lower for comparisons of drug use between EMA and sweat patch methods than for EMA and ACASI methods. The kappa statistics for the comparison of EMA and sweat patch methods were in the moderate agreement range for both cocaine 0.51 (0.44-0.60) and heroin 0.48 (0.38-0.57) use. The agreement in reports between EMA and ACASI methods for cocaine use was 0.59 (0.51-0.67) and heroin use 0.61 (0.53-0.69), which represents moderate and good agreement respectively.

Our comparisons of mHealth methods with biological samples of sweat were concordant (as demonstrated by high percent agreement with EMA) but had lower inter-rater reliability than we would have predicted. The unexpectedly lower number of patches that tested positive for heroin, but not cocaine, suggested a possible misclassification of heroin use by the gold standard.

The level of concordance between EMA and more traditional biological and self-report methods suggests that utilizing EMA mHealth strategies are feasible for assessing drug use among community dwelling, non-treatment seeking chronic drug users. Further, EMA methods remain more flexible and less invasive than drug testing that involves blood, sweat or urine. Additional strengths of EMA methods include their ability to capture both exposure and outcome information in real-time rather than waiting months to be assessed at the next study visit, as well as the ability for data collection to be completed in participant's natural environment rather than in a formal clinic setting. Assessment of drug use by mHealth methods is particularly compelling when considering the strengths, costs and burdens associated with assessing illicit drug use.

In chapter 3, growth mixture models (GMM) were utilized to examine the heterogeneous patterns of daily drug use among participants in EXACT. This analysis examined total drug use on a daily basis rather than on a weekly basis, as was done in chapter 2. Examining daily drug use through GMM found substantial variability in drug using risk among the EXACT population, as evidenced by three

distinct groups of drug users; low, moderate and high intensity drug users. These three drug using risk groups represented individuals with increasing intensity of heroin or cocaine use and whose membership characteristics were distinct.

Compared to those in the low intensity drug using group, those classified as high intensity drug users were younger, less likely to be HIV infected and more likely to share needles and use a variety of drugs including injecting heroin and cocaine separately, together (as speedball) and smoking crack. The high frequency of poly-drug use and needle sharing behaviors of the high intensity drug using group is not only associated with longer time to cessation [7] but puts individuals at risk for the medical consequences of continued drug abuse as well as HIV transmission, acquisition and poor HIV treatment outcomes [8]. The paradoxical reduced HIV prevalence among high intensity users may represent a cohort effect of younger more intense users with distinct social networks from older users [9] who, by nature of declining HIV prevalence have been spared (for now) from acquiring HIV.

The groups discovered through growth mixture modeling had clinical relevance as well. Those classified as high intensity users were found to also be individuals who were likely to fail to attend outpatient medical appointments and were less likely to have health insurance at the visit following the completion of the EXACT study. Participants were not engaging in care possibly because they were currently out of medical care.

Chapter 4 examined the drug-using environment by studying each EMA drug using and craving event for every individual. Our refined assessment of the context of drug use demonstrated that drug use and craving are possibly distinct experiences represented by different social, physical and activity environments. We demonstrated that drug use was facilitated over craving in less structured social and physical environments, such as being in an abandoned space or being around others engaging in drug-related activity. Whereas drug craving without using occurred more frequently in structured physical and social environments, including being with a child, at the doctor's office, or at work.

It has been suggested that craving and relapse may represent independent phenomena and that reports of craving may not predict relapse [10, 11]. However, it is possible that craving represents episodes where individuals have motivation to use but other environmental factors impeded use. Our findings suggest there are different associated factors of craving vs. use but more research is needed to provide evidence that they are distinct entities. Craving in specific environments could lead to use but it is context specific. Building on this premise, our findings suggest that EMA may be utilized to tailor drug treatment interventions. By identifying social, physical and activity environments associated with craving and drug use, drug users could be counseled and supported to avoid such settings and to facilitate time in environments that reduce the probability of drug use.

Lessons Learned

This body of work adds to a growing evidence base that suggests ecological momentary assessment methods are appropriate for assessing challenging and marginalized populations. These EMA data provide extremely valuable information on the proximate influences of drug users' behavior as well as demonstrate the richness of information gained from shortening the data collection interval to minutes instead of months and of locating data collection to occur wherever persons may be, rather than relying on retrospective reporting in a clinic setting. Allowing questions to be responded to in ones' personal environment affords participants the opportunity to answer open and honestly and could increase the integrity of the data collected.

Implementing the EXACT study was met with skepticism regarding the likelihood of success in meeting our objectives of understanding the drug-using environment. We did require a substantial amount of effort from participants in reporting each drug use or craving event and in responding to 5-random prompt surveys a day (a slightly higher participant burden than many EMA studies). Overall, EXACT participants answered 78% of random-prompts, a response rate comparable to other EMA studies performed using similar technologies in varied settings [12, 13]. Studies among populations of illicit drug users, chronic pain patients, smoking cessation and obesity intervention participants all achieved EMA response rates to random-prompt surveys ranging from 70–80% [12, 14-16]. User

fatigue, or exhaustion to responding to device prompts, was another concern of using EMA methods. To examine this potential issue in EXACT, both the percentage of random-prompts answered and the daily mean numbers of responses answered were examined by study week. We found no difference in either the response proportion or average number of daily responses between study weeks [17], suggesting fatigue was not a problem for our participants.

Informal debriefs of participants' experiences in EXACT at the conclusion of the study demonstrated that participants believed study procedures were not overly burdensome or hard to understand. Although we did not conduct formal qualitative evaluations, these debriefs were consistent with our quantitative assessment of participant acceptability, indicating that participants were not over burdened by study procedures or their participation [17].

A concern in using technology for public health research is the rapid evolution and out-datedness of mobile devices. In the EXACT study, the PDA model we used at study initiation was no longer manufactured after 10 months of study recruitment and was largely obsolete by the end of the study. Rapid developments in technology may become a significant barrier to successful implantation and scale-up of mHealth programs in the future. In EXACT, the switch to Android smartphones and the *eMOCHA* platform resulted in more efficient delivery of prompts and automatic data transfer (with the use of cellular data plans), which both enhanced security and minimized data loss. To better address the rapid

changes in technology, alternative approaches to study design must be considered, including designs fitted to the stage of technology or intervention development, adaptive trials and Continuous Evaluation of Evolving Interventions (CEEI) that allow for technology or intervention optimization [18, 19].

An abundance of public health information concerning the drug-using environment, heroin and cocaine use, drug craving, as well as insights into mHealth methods were gained from completing the EXACT study. Following through on this wealth of information must include utilizing these methods for intervention and prevention programs aimed at addressing drug relapse as well as uptake of engagement in care practices.

Future Directions

This dissertation employed EMA methods to develop a comprehensive understanding of the drug-using environment among out-of-treatment drug users. Specifically, we uncovered non-uniformity in the drug using intensity and risk among this population of illicit drug users. Although not part of traditional clinical practice, physicians could begin to routinely ask about a patient's drug use intensity on a daily basis. This question in conjunction with questions concerning drug use history, current mood, and social, physical and activity environments would provide clinicians with a deeper understanding of the drug using patterns of their patients, help in predicting relapse as well as the likelihood of ART

adherence among HIV infected drug users. Long-term clinical goals of this work include incorporating EMA data directly into electronic medical records (EHR).

The EXACT study provided a deeper understanding of the proximate influences of drug use, which could allow for tailored interventions. Ecological Momentary Interventions (EMI), are interventions provided in real-time and are carried out in participant's natural environments with the goal of real-time behavior change.

EMIs are delivered in many forms using features of mobile devices including text messaging, photographs and videos. Interventions can be delivered to participant's phones as unstructured passive clinical recommendations throughout the day (e.g., breathing techniques for individuals who suffer from anxiety [20] or promoting physical activity for underactive adults [21]). These interventions remind individuals of useful techniques for handling daily health matters as well as provide them with tools to achieve healthier lifestyles. Structured interventions may include formalized clinical advice for patients with specific medical needs at critical times (e.g., participants in smoking cessation programs receiving text messages with tips for dealing with cravings during periods when smoking is often reported [22]). These structured interventions are informed by the patterns and timing of individual behaviors that have been previously uncovered from EMA analyses [23]. Although many studies have shown treatment gains immediately or shortly after the intervention, there remains conflicting evidence regarding the

maintenance of effects when using text messages alone for the intervention. Furthermore, these passive interventions may not be suitable for high-risk populations.

Newer forms of ecological momentary interventions involve the use of location-based technologies embedded in all smart phones. Geographical positioning systems (GPS), altimeters and pedometers are now routinely incorporated into smart phones. These time stamped features have begun changing how interventions are delivered and will continue to evolve as our understanding of human moment grows. Our understanding of the real-time drug-using environment must be updated to include how time and space play a role in drug use and craving and how individuals experience fluctuating exposures within a single day and within varying environments. Ecological momentary interventions that are associated with GPS movements as well as time of day, day of week and time of month of drug use and craving must still occur in natural environments at identified moments in everyday life, allowing EMI to provide real-time support in the real world.

For example, it is well understood that substance abuse is a disease marked by frequent relapse and for most, a life-long struggle. Whether an individual attended inpatient treatment or not, regular on-going check-ups to assess the severity of abuse is atypical after an overdose. This scarcity rises as marginalized

disadvantaged communities struggle to access an already strained treatment system, face the cost of medical insurance and regular appointments necessary for on-going care. However, with the use of smart phones, treatment support and drug monitoring could be available almost constantly. Personalized care is possible at the moment of greatest need. Patients could be monitored passively and if they wander into an area where they previously reported using drugs their smartphone could ask why they are in that location, provide them an alternate route to walk or provide them emotional support for dealing with a drug craving in real-time.

An example of this is an intervention that was recently completed in the Addiction-Comprehensive Health Enhancement Support System Study (A-CHESS) [24]. A randomized clinical trial of patients leaving 3 Midwestern residential treatment programs for alcohol abuse provided participants in the intervention group with a smartphone with the A-CHESS application. The application had both a static component (audio-guided relaxation) and interactive features. For example, if a patient neared a high-risk location, such as a bar she used to frequent, the GPS system initiated an alert asking the patient if they wanted to be there. On a weekly basis, participants also completed a questionnaire related to risky drinking and if the risk score exceeded a certain threshold, A-CHESS automatically sent notifications to counselors. Results demonstrated that over the previous 30 days at 4, 8 and 12 months post residential treatment, those who received the A-CHESS application reported a lower mean number of risky

drinking days and a higher likelihood of consistent abstinence than those who received treatment as usual. As one of the few health care applications tested rigorously, A-CHESS provides promising results for sustained patient behavior change for future studies involving substance-using populations.

Additionally, continuation of EMA self-reports of drug use could allow clinical staff, nurses or trained peer navigators to monitor individuals' drug use and craving. Peer navigators are typically individuals who have similar backgrounds and past experiences as those they are guiding, thereby providing access and credibility not easily achieved by medical professionals [25]. Previous studies have demonstrated the potential for peer-based interventions to increase adherence to medical care for active persons who inject drugs [26] and our group is currently working on a project entitled "Technology-Enhanced Peer Navigation to Improve Injection Drug Users Engagement in HIV Care" with the hopes of establishing the feasibility and acceptability for a novel mHealth intervention to improve adherence and retention in care for HIV-infected drug users. These trained individuals would monitor EMA responses and contact patients if there were drastic changes in drug using behavior (e.g., high spikes over a weekend) and help guide and counsel patients with their drug-related problems. The two-way communication is the hallmark of ecological momentary assessments and interventions. These EMI methods would continue to allow patients to be under the care of a physician but with less cost and burden to the participant and a shift

in treatment and care routinely provided by the physician compared to a mid-level provider or peer.

Assessment of drug use in epidemiologic studies can be enhanced through mHealth strategies. Capturing drug use optimally will involve an approach that is unobtrusive, does not rely on recall, has limited requirements for participant participation, and that is readily accessible and affordable. Remote monitoring with wearable sensors is currently under evaluation to determine if sensors can identify the onset and duration of cocaine use. iMStrong (PI Edward Boyer, Univ of Massachusetts) is a system comprised of an unobtrusive, wearable sensors that continuously record and wirelessly transmit physiologic measures (e.g., increased electrodermal activity, skin temperature, and motion) of sympathetic nervous system arousal that works with a smartphone to alert individuals to the onset of drug cravings. Similarly, “AutoSense” involves an unobtrusive, wearable sensor that can collect heart rate, respiration patterns and blood alcohol levels in the natural environment of any person who is wearing the sensor [27]. These methods for real-time quantification of alcohol and cocaine use could be adaptable to measuring other illicit substances in non-clinical settings.

Figure 5.1 describes the framework for future directions of this work as well as a system that uses the contextual information gained from EMA combined with newer mHealth technologies. More detailed EMA data can be collected through

the use of common features of a smart phone (photographs and videos) while geo-tracking technologies (GPS monitoring and accelerometers) and biosensors worn on the body (real-time sensing of metabolites and physiology) would enhance our understanding of the drug using environment, gather more detailed data in real-time and be used for interventions.

Conclusions

The field of mHealth remains largely stuck in the land of “apps on a phone” and generally lacks rigorous evaluation. Bringing mHealth interventions to scale requires initial feasibility studies, like the EXACT study, followed by larger trials to test the effectiveness of mHealth approaches to optimizing care. Ecological momentary assessment methods do hold promise for reaching and characterizing high-risk drug using populations, as several studies have demonstrated these populations are capable of utilizing mobile devices to repeatedly describe their behaviors.

The uptake of mHealth methods and interventions holds even greater potential as more individuals receive insurance coverage due to the new Patient Protection and Affordability Act in the United States. Ecological momentary assessments and interventions and sensors should become economically viable as more individuals become insured and potential offsets in the cost of smartphones and data plans are

made available. The results of this dissertation underscore the benefits of changing how epidemiologic data can be collected and assessed in real-time, and demonstrate the ability of poly-drug using individuals to provide behavioral data in their daily life, allowing for a novel and more precise method for characterizing the drug using experience and designing tailored interventions to mitigate the consequences of drug use.

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Table 5.1: Assessment of illicit drug use via Ecological Momentary Assessment, Audio Computer-Assisted Self-Interview and Sweat Patch

	<i>Method of drug use assessment</i>		
	Ecological Momentary Assessment (EMA)	Audio Computer-Assisted Self-Interview (ACASI)	Sweat-Patch
What device is used to capture drug use?	Mobile Phone, Tablet or Hand-held device (e.g. Personal Digital Assistant)	Computer or Lap-top	<i>PharmChek®</i> Sweat Patch
How is drug use captured?	Participants self-cue and self-report in real-time through the device	Participants are asked to recall drug use behaviors and self-report through the computer	Participants wear the sweat patch and drug metabolites secreted in sweat are captured on the patch
Is internet access necessary?	Not necessarily; Responses can be stored on the device and transferred at study conclusion, OR responses can be pushed to a server if wireless internet is available	No, data is captured and stored on a computer	No
How often do participants visit study site?	For studies with short follow-up (e.g. less than 30 days) participants may only need to visit the study site to pick-up and drop off the device and responses to survey questionnaires are done in the participant's natural environment. This depends on the other requirements of the study (e.g. if weekly biological samples are needed)	ACASI interviews typically take place at study sites and are required as often as the study protocol requires. For example, for studies requiring semi annual follow-up, participants return to the study site twice a year to answer questions via ACASI. If the participant does not attend the study visit, the data is missing for that visit	Sweat-patches can be worn for up to 10 consecutive days. The sweat-patch captures drug metabolites for the duration of time the patch is worn. Participants must visit the study site for the patch to be put in place and removed. Depending on the study protocol, this could be as frequent as every 2-3 days.
How long does assessment take?	Participants self-initiating an event survey concerning the outcome of interest will also most likely answer questions concerning the context of the event, e.g. who were you with, what were you doing, what were you feeling. The EXACT survey took approximately 5 mins. The same questions are asked each time a participant self-reports	Because interviews are often spaced out over months, an ACASI survey will ask more questions that are over arching	The patch can be worn continuously for up to 10 days

Table 1: Assessment of illicit drug use via Ecological Momentary Assessment, Audio Computer-Assisted Self- Interview and Sweat Patch (cont.)

Expense	Cell-phones, airtime and data plans are necessary to collect EMA data. Prices vary by cellular carrier. Remuneration is also necessary for participation. The EXACT study cost approximately \$427.33 per participant, or \$15.29 per day of 30 days of follow-up (this price includes the GPS devices participants were also required to carry as well as survey development)	One time cost to purchase the computer and software to run ACASI (\$1500-\$4000). Cost depends on number of questions and if translation is necessary. A dedicated computer is often required for ACASI surveys. Remuneration for participation	Cost to attain and test sample varies by the number of drugs tested per patch. Price increases if repeated measures are required. Often, samples are processed in external labs. For EXACT: \$540.00 for 50 patches, \$25.00 for protective covers and \$21.00 to test each patch. Per person: approximately \$131
Participant Burden and ramifications	Participants must remember to report every occurrence of drug use or drug craving. It is expected participants will report daily and therefore with so many responses from each participant, the effect of missing or forgetting to report an event (or a few events) has less of a consequence on the ability to use the data to make accurate inferences	Returning to the study site for each interview can be difficult for some participants, especially if they lack access to a car or are working. The ramifications of missing even a single study visit may affect data quality and the ability to make accurate inferences	The patch must be worn 24 hours a day and may become uncomfortable. If the sweat patch is removed it cannot be put back on to resume drug metabolite capture. If the patch is tampered with, data concerning duration of drug use is lost.
Possible biases/misclassification	Social desirability bias and user fatigue. Over and under reporting of activities is likely and this is a common problem when asking participants to describe specific illicit behaviors. The use of devices for a long period of time may lead to user fatigue and attrition in reporting.	Social desirability bias and recall Bias. Recall biases arise when cohort studies require participants to recall their drug using behaviors from the previous study visits (sometimes 6-months apart). This leads to under and over reporting behaviors	The sweat patch may affect the behaviors of participants and therefore may not capture the true drug using history leading to misclassification biases
How does this method overcome the possible biases?	A hallmark of EMA data collection is ability to reduce social desirability bias by providing participants with devices in which they can report their drug use when it occurs in their natural environments outside of a study visit. User fatigue can be assessed and follow-up times adjusted to ensure participants report their behaviors	The purpose of ACASI is to allow participants to answer questions concerning illicit behaviors using the computer rather than in a face-to-face interview to reduce social desirability bias. Additionally because the survey is read aloud by the computer, literacy is not a concern.	This method can not guarantee participant compliance

Figure 5.1: Future directions of EMA and mHealth research

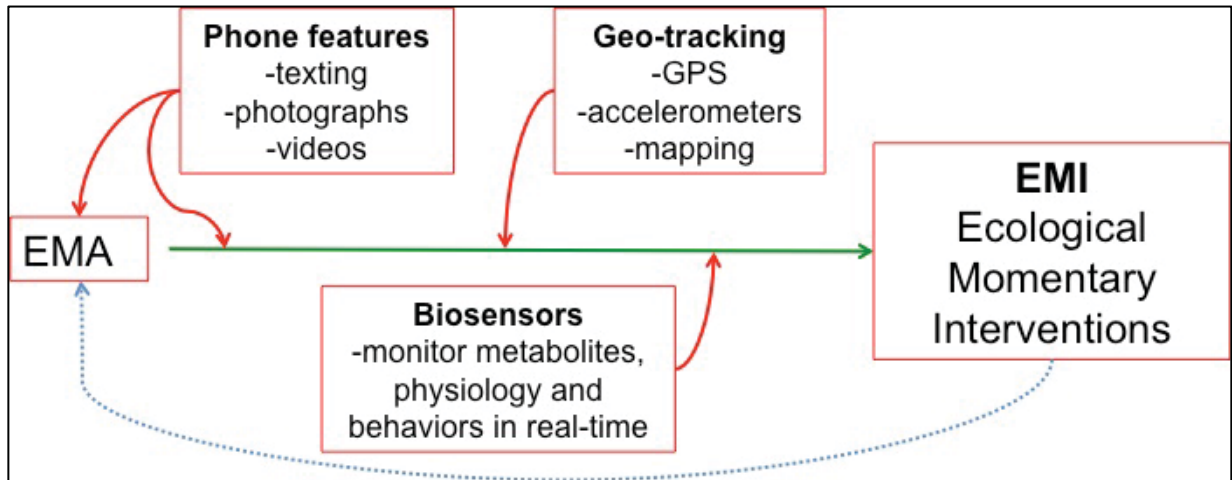


Figure 5.1: EMA methods currently provide real-time data on an individual's environment and behavior. A system that is unobtrusive and uses additional features of the phone as well as geo-tracking applications and biosensor technologies will provide an even deeper understanding of individual movement and behavior in real time, which can be used for ecological momentary interventions.

Curriculum Vita

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EDUCATION

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Doctor of Philosophy in Epidemiology, June 2014

GPA: 3.8

Concentration: Infectious Disease Epidemiology

Thesis: *Mobile Health (mHealth) Assessment of Illicit Drug Use Among Community Dwelling Injection Drug Users, Baltimore, MD.*

Funding: Pre-doctoral fellow, HIV Epidemiology and Prevention Sciences Training Program (T32, PIs: Dr. Chris Beyrer and Dr. Shruti Mehta) 2013-present
The Dorothy and Arthur Samet Student Support Fund in Epidemiology, 2013
Epidemiology Doctoral Thesis Research Fund Recipient, 2013

Honors: The Charlotte Silverman Award for Scholarly Work in Epidemiology for improving the health of communities, 2012

Activities: Epidemiology Department Partial PhD Tuition Scholarship, 2011-present
JHU Global mHealth Initiative Student Leadership *President* 2012-present

The first mHealth PhD graduate from the JHU Global mHealth Initiative
Epidemiology Student Organization, *Doctoral Student Representative 2011-2012*

Advisor: Gregory Kirk, MD, PhD, MPH

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Master of Health Science in Epidemiology, May 2010

GPA: 3.8

Concentration: Infectious Disease Epidemiology

Thesis: *Incidence and Predictors of Pregnancy Among HIV-Infected and Uninfected Women in the Women's Interagency HIV Study from 2002-2009*

Funding: Epidemiology Departmental Scholarship for Academic Achievement, 2009-2010

Honors: Trudy Bush Award for Outstanding Work in Women's Health, 2010

Activities: Epidemiology Student Organization, *Representative to Student Assembly*

Advisors: Susan Sherman, PhD, MHS and Elizabeth Golub, PhD, MPH

BRANDEIS UNIVERSITY, Waltham, MA

Bachelor of Science in Health: Science, Society and Policy, May 2004

Bachelor of Arts in Biochemistry, May 2004

GPA: 3.52

Honors: *Cum Laude*

Dean's List

Brandeis Roosevelt Fellow

Undergraduate Department Representative

Completed Pre-Medical Academic Track

Activities: Brandeis Student Health Initiative, *Founder and Director*

SKILLS

Software Proficiencies: Statistical Analysis (SAS, STATA, basic R)

Mapping (ArcGIS)

Microsoft Office (Excel, PowerPoint and Word)

Database Research: PubMed/Medline

Languages: Web of Science
English (native)
French (conversational)

RESEARCH EXPERIENCE

EPIDEMIOLOGY DEPARTMENT, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Research Analyst, The AIDS Linked to the IntraVenous Experience (ALIVE) Study, July 2010-Present

Mentor & Principal Investigator: Dr. Gregory Kirk

Conceptualized and analyzed real-time Ecologic Momentary Assessment (EMA) (mHealth) data to understand the drug using environment and its impact on engagement in care outcomes. Utilizing data from the ALIVE study, analyzed mean community viral loads in HIV-infected injection drug users to understand its association with HIV incidence and examined longitudinal patterns of sleep disturbances.

HEALTH BEHAVIOR SCIENCES DEPARTMENT, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Research Assistant, Lighthouse Studies @ Peer Point, March 2013-present

Mentors: Dr. Cui Yang

Helped develop the research study plan, survey questions and IRB protocol for a mHealth study utilizing Ecologic Momentary Assessment (EMA) methods to examine alcohol use patterns and behaviors in real-time among African American men who have sex with men. Perform statistical analyses examining correlates of real time alcohol use and HIV risk

THE GSMA DEVELOPMENT FUND, Cape Town, South Africa

mHealth Impact Intern, Summer 2012

Mentor: Dr. Craig Friderichs

Reviewed and validated methodological approach to the Impact Pathway for the mHealth component of GSMA's Mobile and Development Intelligence (MDI) data portal. Aided in creating a framework by which to review and include mHealth research and literature. Compiled, reviewed and catalogued evidence found in literature on mHealth for the MDI data portal.

HEALTH BEHAVIOR SCIENCES DEPARTMENT, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Data Manager and Staff Interviewer, BESURE Study, June 2009-February 2011

Mentor & Project Investigator: Dr. Danielle German

Responsible for organizing site data and liaising with the Centers for Disease Control to produce accurate data reports for this cross sectional National HIV Behavior Surveillance study among groups at high risk for HIV in Baltimore City. Interviewer responsibilities include assessing study eligibility and conducting interviews with injection drug users on drug use and HIV risk.

HEALTH BEHAVIOR SCIENCES DEPARTMENT, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Research Assistant, Lighthouse Studies @ Peer Point, March 2009-May 2010

Mentors: Dr. Carl Latkin and Dr. Melissa Davey-Rothwell

Analyzed baseline data for the CHAT project, a social-network based HIV/STD prevention study guided by the theories of social influence and cognitive dissonance. Examined economic indicators and risk for HIV infection

BUREAU OF EPIDEMIOLOGY SERVICES, NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE,

New York, NY

Special Assistant to Assistant Commissioner Dr. Bonnie Kerker, October 2006-July 2008

Compiled data on monthly indicators for Commissioner of Health. Collected data for Injury Surveillance System and administrated the Youth Risk Behavioral and Community Health surveys. Coordinated and data managed Department of Corrections/Department of Homeless Services inter-agency project.

ERNST LABORATORY FOR INFECTIOUS DISEASE RESEARCH, NYU SCHOOL OF MEDICINE, New York, NY

Research Assistant, July 2004-October 2006

Mentor: PhD candidate Andrea Wolf

Infected raw cells and over-expressing Class II Transactivating raw cells with both live Mycobacterium tuberculosis (M.tb) as well as gamma irradiated M.tb and assayed T-cell production of Interferon gamma. Studied antigen presentation pathway of raw cells and the role of Cathepsin S in processing antigen.

TEACHING EXPERIENCE

Lead Teaching Assistant: Epidemiologic Methods 2, August 2011-December 2011

Mentors: Drs. Gypsyamber D'Souza and Milo Puhon

Aided in redevelopment of course lectures and labs and was responsible for writing both the mid-term and final exams. Served as resource for students regarding course content. Graded student work.

Course Development and Teaching Assistant: Observational Epidemiology, June 2009-March 2010

Mentor: Dr. Elizabeth Golub

Aided in redevelopment of course structure and design. Served as resource for students regarding course content. Graded student work.

Teaching Assistant: Epidemiology and Public Health Impact of HIV and AIDS, September 2009-December 2009

Mentor & Professor: Dr. Homayoon Farzadegan

Responsible for course organization and speaker schedules. Served as resource for with students regarding course projects and examinations. Graded student work.

BRANDEIS UNIVERSITY, Waltham, MA

Undergraduate Chemistry Teaching Assistant, September 2003-May 2004

Ran weekly lab sessions and experiments. Taught and graded students on basic lab techniques.

VOLUNTEER EXPERIENCE

STUDENT OUTREACH RESEARCH CENTER (SOURCE), JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, Baltimore, MD

Amazing Grace Volunteer, Spring 2013

Helped East Baltimore Lutheran Church mulch, plant and landscape it's urban vegetable garden

HOUSING WORKS, INC. New York, NY

Bookstore Volunteer Team Leader, January 2005-July 2008

Trained new volunteers at volunteer-run used bookstore, as part of the nation's largest non-profit AIDS advocacy organization.

COLORADO AIDS PROJECT, Denver, CO

Summer Intern, Summer 2003

Provided assistance to underserved clients in finding housing, transportation and food.

PUBLICATIONS

Linás, BS, Latkin C, Westergaard RP, Chang LW, Bollinger RC, Genz A, Gregory KD. Capturing Illicit Drug Use When and Where it Happens: an Ecologic Momentary Assessment of the Social, Physical and Activity Environment of Using versus Craving Illicit Drugs. Under review at *Addiction*

Kirk GD, **Linás BS**, Westergaard RP, Piggott D, Bollinger RC, Chang LW, Genz A. The Exposure Assessment in Current Time (EXACT) Study: Implementation, Feasibility and Acceptability of Real-Time Data Collection in a Community Cohort of Illicit Drug Users. *AIDS Research and Treatment*, 2013 Article ID 594671, 10 pages

Genz A, Kirk GD, Piggott, D, Mehta SH, **Linás BS**, Westergaard, RP. Uptake and acceptability of information and communication technology in a community-based cohort of people who inject drugs: Implications for mobile health interventions. Under review at *The Journal for Medical Internet Research*

Davey-Rothwell M, **Linás BS**, Latkin C. Sources of personal income and HIV risk among sexually active women. *AIDS Education and Prevention*, 2012 24(5): 422–430

Kirk, GD, Astemborski J, **Linás BS**, Lau B, Celentano DC, Galai N, Mehta SH, Vlahov D. Population Viral Load, Antiretroviral Therapy Uptake and HIV incidence: Evaluation of Treatment as Prevention in a Community-Based Cohort Study of Injection Drug Users: 1988-2009. *Submitted*

Linás BS, Minkoff H, Cohen M, Karim R, Cohan D, Wright R, Young M, Watts DH, Golub ET. Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002-2009. *AIDS*, 2011 25(5): 707-11

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Andrea J Wolf, Ludovic Desvignes, **Beth Linás**, et al. Initiation of the Adaptive Immune Response to M. Tuberculosis Depends on Antigen Production in the Local Lymph Node, Not the Lung. *Journal of Experimental Medicine*, 2008, 205:105-15.

Wolf, A.J., **Linás, B.S.**, Giralдина J., et al. Mycobacterium tuberculosis Infects Dendritic Cells with High Frequency and Impairs Their Function in Vivo. *Journal of Immunology*, 2007, 179:2509-2519

ABSTRACTS

Oral Presentation, *Capturing illicit drug use when it happens: an ecologic momentary assessment of drug users and their environment*, mHealth Summit 2013, Washington DC: December 2013

Oral Presentation, *Capturing illicit drug use when it happens: an ecologic momentary assessment of drug users and their environment*, Wireless Health Conference, Baltimore: November 2013

Oral presentation, *The EXACT Study: Exposure Assessment in Current Time. Ecologic Momentary Assessment of drug use in daily life*, mHealth Summit, Washington DC: December 2011

First Author Poster Presentation, *HIV Infection and Illicit Drug Use are Associated with Severe Sleep Disturbance*, Conference on Retroviruses and Opportunistic Infections, Boston, MA: February 2011

Oral Presentation, *Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002-2009*, Late Breaker Epidemiology Section, American Public Health Association Conference, Denver, CO: November 2010

First Author Poster Presentation, *M. tuberculosis* inhibits class II antigen presentation by mechanisms independent of blocking class II induction by interferon gamma, American Association of Immunologists Annual Conference, Boston, MA: May 2006